

Nicotinamide as independent variable for intelligence, fertility, and health

Williams, Adrian C; Hill, Lisa J

DOI:

[10.1177/1178646919855944](https://doi.org/10.1177/1178646919855944)

License:

Creative Commons: Attribution-NonCommercial (CC BY-NC)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Williams, AC & Hill, LJ 2019, 'Nicotinamide as independent variable for intelligence, fertility, and health: origin of human creative explosions?', *International Journal of Tryptophan Research*, vol. 12, pp. 1-15.
<https://doi.org/10.1177/1178646919855944>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Williams, A. C., & Hill, L. J. (2019). Nicotinamide as Independent Variable for Intelligence, Fertility, and Health: Origin of Human Creative Explosions? *International Journal of Tryptophan Research*. <https://doi.org/10.1177/1178646919855944>

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy


While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Nicotinamide as Independent Variable for Intelligence, Fertility, and Health: Origin of Human Creative Explosions?

Adrian C Williams¹ and Lisa J Hill² 

¹Department of Neurology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK. ²School of Biomedical Sciences, Institute of Clinical Sciences, University of Birmingham, Birmingham, UK.

International Journal of Tryptophan Research
Volume 12: 1–15
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1178646919855944


ABSTRACT: Meat and nicotinamide acquisition was a defining force during the 2-million-year evolution of the big brains necessary for, anatomically modern, *Homo sapiens* to survive. Our next move was down the food chain during the Mesolithic 'broad spectrum', then horticultural, followed by the Neolithic agricultural revolutions and progressively lower average 'doses' of nicotinamide. We speculate that a fertility crisis and population bottleneck around 40 000 years ago, at the time of the Last Glacial Maximum, was overcome by *Homo* (but not the *Neanderthals*) by concerted dietary change plus profertility genes and intense sexual selection culminating in behaviourally modern *Homo sapiens*. Increased reliance on the 'de novo' synthesis of nicotinamide from tryptophan conditioned the immune system to welcome symbionts, such as TB (that excrete nicotinamide), and to increase tolerance of the foetus and thereby fertility. The trade-offs during the warmer Holocene were physical and mental stunting and more infectious diseases and population booms and busts. Higher nicotinamide exposure could be responsible for recent demographic and epidemiological transitions to lower fertility and higher longevity, but with more degenerative and auto-immune disease.

KEYWORDS: neolithic, neanderthal, disease transitions, demographic transitions, immune tolerance, 'K-selection', 'r-selection', fertility, domestication

RECEIVED: April 25, 2019. **ACCEPTED:** May 3, 2019.

TYPE: TRY-12 Tryptophan supplements: History, Potential Advantages and Toxicity: Review

FUNDING: The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by QEHB Charity, Birmingham, UK.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Adrian C Williams, Department of Neurology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2WB, UK. Email: Adrian.Williams@uhb.nhs.uk

'... we essay to create a second world within the world of nature'.

Cicero

'... thoughts about food in prehistory are changing with a proper combination of the theoretical and the technical ...'.

Gosden¹

Introduction

Scholars from the 18th century, namely, Turgot, Montesquieu, de Tocqueville, Adam Smith, and later Childe, McNeill, Crosby, and Diamond recognised an interesting set of correlations involving the basic mode of food subsistence (including alcohol, psychedelic and medicinal compounds) and a broad set of human characteristics. Their insights and speculations were derived primarily from observing hunter-gatherers, farmers and pastoralists, the 'Columbian exchange', and modernity.^{2–8} Such characteristics included population density, divisions of labour, the economy and technology, social norms, rituals and institutions, and the emergence of disease and war. How key dietary variables work proximally to effect success or failure through individual metabolism and physiology has not been elucidated, although mitochondria and the need for prodigious amounts of adenosine triphosphate (ATP) get a mention.^{9–14}

Nicotinamide and Evolution

Nicotinamide and nicotinamide adenine dinucleotide (NAD)-based hydrogen (H) metabolism can be traced to the origins of life, specifically multicellular life with the symbiotic acquisition

of mitochondria and the preferential use of oxygen (as electron acceptor) for maximal ATP production. NAD can be synthesised from tryptophan, but the preferred source is dietary nicotinamide. Nicotinamide has a detoxification pathway via NNMT that links to methyl metabolism. Nicotinamide adenine dinucleotide consumers control metabolism, and NAD sensors drive the quest for food and construction of an NAD world^{15–19} (Figure 1).

An evolutionary account of the nicotinamide supply may be an ecological flashlight to explain our history. Brillat-Savarin's aphorism states 'The destiny of nations depends upon the manner in which they nourish themselves' as others have also implied.^{20–27} Quests for meat and plants, based on communal knowledge and manipulation of nature, is one of our defining features.^{28–68} Nowadays, money hand-outs to the poor get preferentially spent on meat and trump other welfare programmes, as Engel first pointed out happens whenever wages rise^{69–73} (Figure 2).

Early hominids speciated in an unstable climate, driven by solar radiation and tectonic activity, that produced rifts with varied and varying habitats. We left shrinking forests for savannahs, lakes, and shorelines that allow for more game and plant produce. Food drove our global expansion, perhaps at some cost to Megafauna, and later drove empires and colonial settlers for lands to farm to secure dietary balance^{33,74–96} (Figure 3).

If population densities had remained at hunter-gatherer levels of 0.05 per km², global population would now be 7 million,



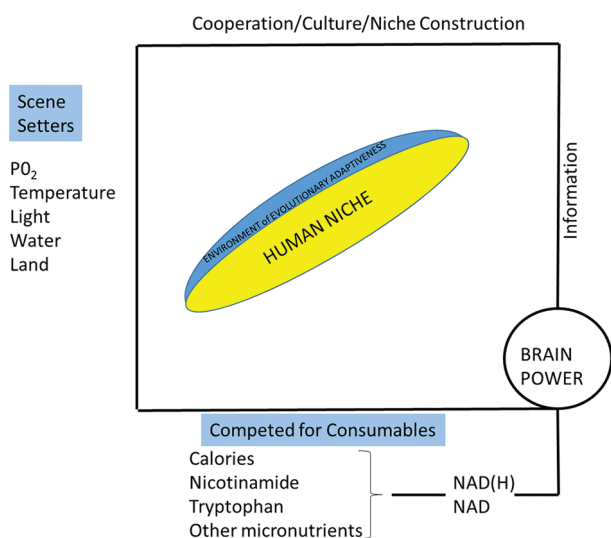


Figure 1. Scene setters are not a given but oxygen varies little (except by altitude) and is free. NAD supplies, by contrast, required brains and overcoming dangers in hunter-gatherer days and now have high (financial) costs that can be prohibitive. NAD indicates nicotinamide adenine dinucleotide.

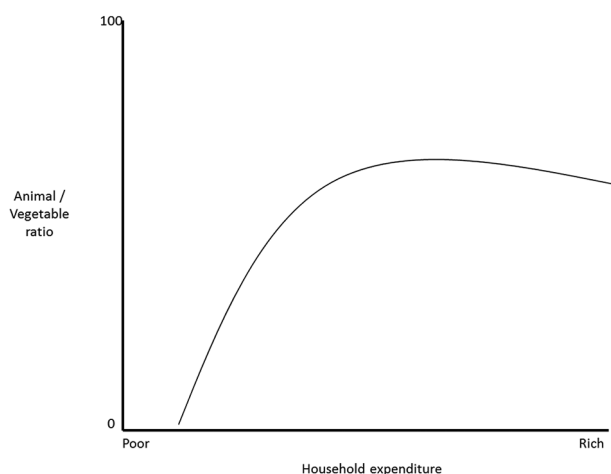


Figure 2. Engel curve showing increased proportion spent on meat as wealth increases.

not 7 billion and rising. Much of the evidence about the fertility (and disease) explosion at the time of the Neolithic is derived from skeletal and genetic data.^{27,97,98} No form of contraception, infanticide, or extended breast feeding explains easily these low fertility states or, for that matter more recent declines in fertility that tellingly start with high meat intake whether by country or by social strata.^{99–128} Our trophic level is highly variable. We argue the variances that emerged as we moved down the food chain originally had positive reasons by creating small intellectual classes and larger labour i.e. work-forces with higher fertility, but such variances are now too extreme, no longer necessary, and may be dangerous^{129–153} (Figure 4).

Omnivore or Super-Omnivore

We are (super) omnivores as much of our culture, creative minds, behavior, and many local riddles over food preferences

and taboos, can be seen in the light of omnivory.^{154,155} Anthropologists have deciphered that the preferred diet is a very simple A + 2B (meat and 2 vegetables).¹⁵⁶ There have always been considerable variances depending on season and latitude being less plant-based at the poles – (economics now, however, being more important than geography). Local conditions favoured a variability package aided by technology and tools, use of fire, fermentation, cooking, and xenobiotic biochemistry to cope with toxins or nutrigenomic developments to deal with lactose in adult life and more starch.^{157–160} ‘Pharmacophagy’ included hallucinogens and medicines allowed some control of fertility. Triangulating diet with detailed environmental information and social collaboration led to further experiments with fertility and its trade-offs.^{161,162} Societies created (neuro)chemical and endocrine profiles as nicotinamide and tryptophan affect dopamine, serotonin, immunologic, and reproductive pathways^{163–167} (Figure 5).

First: Meat Obsessed

Endurance running and technology with problem-solving, social skills, and language helped to capture meat.^{168–170} Consciousness helped create ‘a second world within the world of nature’ by allowing a sense of purpose in sourcing our supplies. Even recognising the inevitability of death and the need to reproduce for a communal after-life helped to concentrate minds using high-energy interneurons and pyramidal neurones with their oscillating networks (that are lost in cases of pellagra).^{171–175}

Our primate dietary history previously tacked between insectivores, frugivores, herbivores, and near-carnivores back to omnivores. Hunting and sharing meat between the sexes and ages was a feature of all early societies.¹⁷⁶

High Intelligence Was Originally Necessary to Survive

Separating foraging cognition, ecological, domain-specific intelligence, and social brain hypotheses may be unhelpful dichotomies as our general intelligence may seamlessly span all functions necessary for food and reproductive needs. Spatial memory, reasoning power, and patiently solving complex ecological challenges to put meat on the shared menu served at a central-place in a risky and fluctuating environment was required.^{177–181} ‘The Great Acceleration’ putting us in charge of the ‘Anthropocene’ is based on an omnivorous diet and domesticated ‘Walking Larders’ with a central role for adequate nicotinamide and high intelligence.^{182–185}

Nicotinamide Deficiency

Nicotinamide is sourced from meat and milk with contributions through gathering sea-shell foods, eggs, insects, and nuts. Both meat and carbohydrate hungers are accepted, but the real drive may have been for a ‘Goldilocks’ balance between animal and plant produce. Nicotinamide adenine dinucleotide deficiency was recognised as causing arrested evolution and atavistic degeneration by the Italian pellagra specialist Lambroso in 1860 and responsible for down-shifts in culture and behaviour.

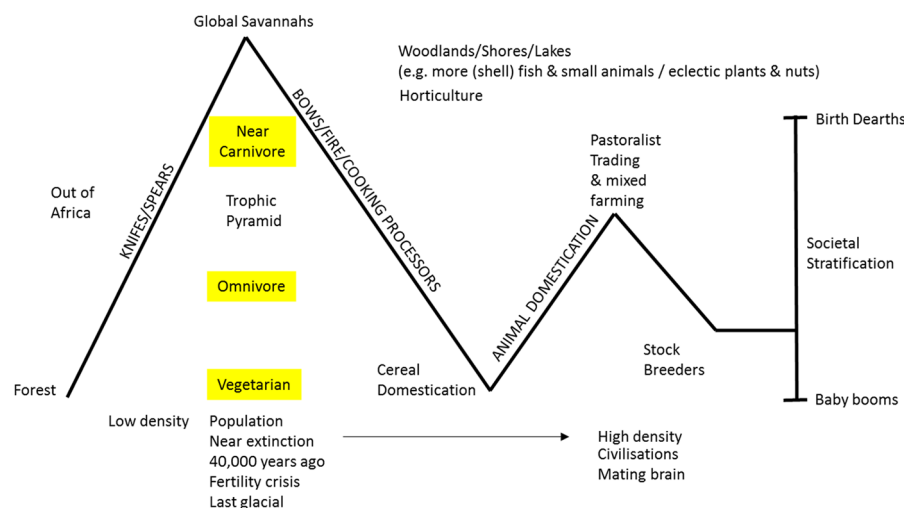


Figure 3. Early 'Up's and Down's' and then oscillations on the trophic pyramid. Every move alters nicotinamide/tryptophan metabolism.

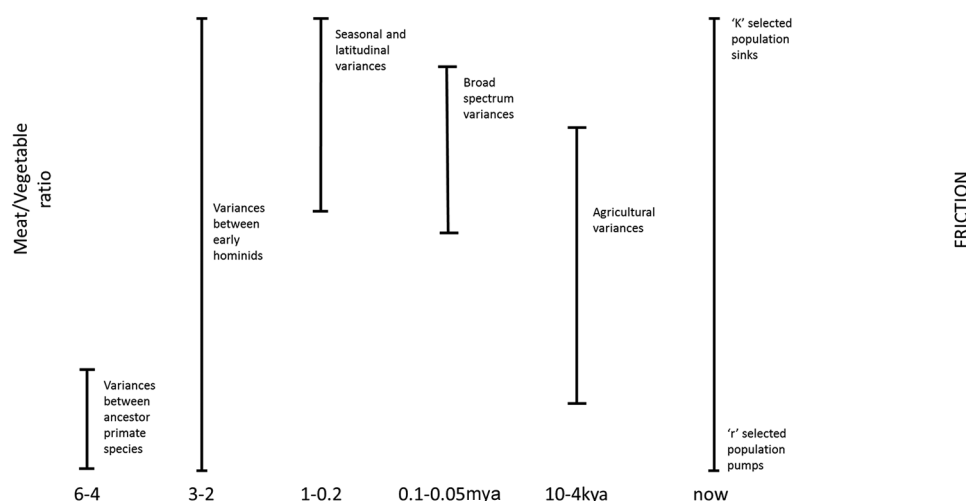


Figure 4. Meat: cereal/vegetable variances over our history. These variances are now extreme going beyond homeostatic controls even with the help of symbionts.

The earlier move down the food chain in the Neolithic indeed led to a decline in height and the emergence of many infectious diseases and bone and oral ill-health. Both the pellagra epidemics and observations on hunter-gatherers denied their right to hunting demonstrated the profound de-humanisation of human beings and their social networks under these circumstances that also resulted in cases of cannibalism – some sanctioned by states and religions where the meat supply was poor such as the Aztec empire.^{186–189} Changes from pastoralism to reliance on a maize crop or imports have been recapitulated in many parts of Africa with similar effects on health and behaviour. However, 'rabbit starvation' described in Arctic explorers shows that meat and excess protein can also be toxic and needs to be balanced with adequate carbohydrates.

Chronic meat and therefore nicotinamide deficiency was likely at the time of the Neolithic transition, allowing the rise of symbionts that can act as back-up, including TB and perhaps leprosy and malaria that later disappear.^{190–197} Unsuccessful quests may have led to stunting of *Homo naledi* (not found with evidence

of hunting) or *Homo floresiensis* (as islands have restricted availability of meat), as happens to forest pygmies.^{198–208}

Plague After Plague and Still Plagues of Corn

The pellagra literature includes evocative titles such as 'A Plague of Corn' or 'Maize for the Gods' suggesting that cereals are a mixed blessing. Defined epidemics of pellagra, diagnosed by a characteristic rash with gut infections and a full gamut of neuropsychiatric disease, occurred from the 18th century, notably in Southern Europe and America, up till the modern day; usually now relating to war and refugees, but all these epidemics may be the tip of an iceberg. Earlier, pellagra may have been responsible for the reports of 'leprosy' in the Old and New Testaments on poor 'manna' diets – and modern leprosy is of interest as nicotinamide can cure it (as it can also cure TB). Later, pellagra may be underdiagnosed or called 'environmental encephalopathy' or simply mental or physical stunting and a poor constitution. Reliance on cereals affects those in (meat) poverty, particularly in Africa where the 'hidden hunger' of

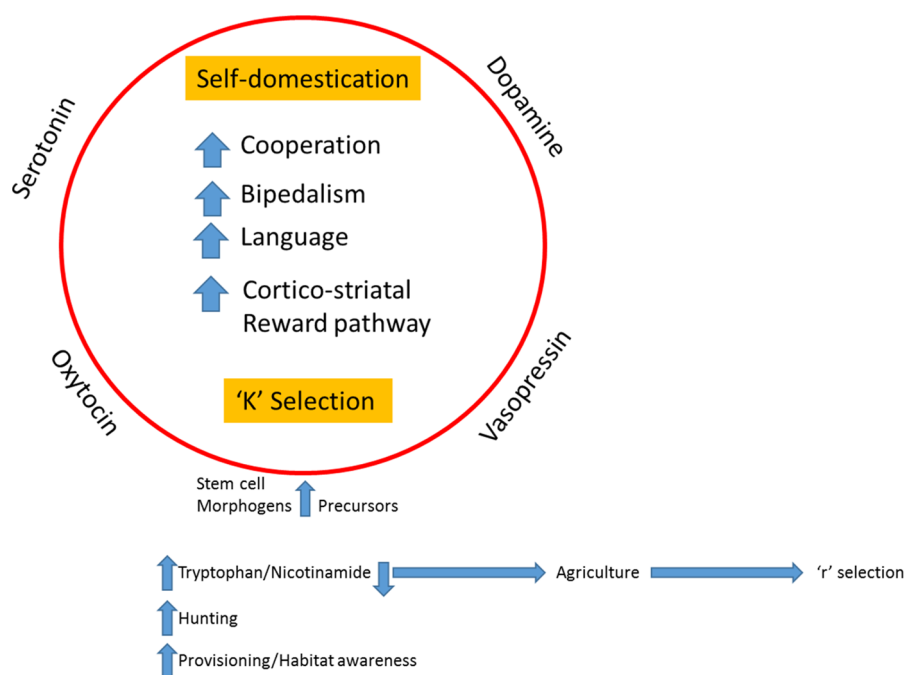


Figure 5. Prosocial personality and neurochemical evolution involving serotonin and dopaminergic was driven by diet. An early emphasis on 'K' selection in our line was later balanced by a change back to a more plant based diet enabling 'r' selection when required.

micronutrient deficiencies is rife that conspires to exacerbate other insults (such as TB and HIV) to cause disease.^{209–236}

Recently, talk has been about integrating diet and the microbiome, concentrating not so much on specific foods or taxonomical identities as their functional competencies, and contribution to providing micronutrients, including vitamin B3, as meta-genomic units of selection and fitness. The epidemics of pellagra are a good example of what can happen when this co-operation goes wrong, leading to dysbioses and uncontrolled autophagy and consequent degeneration. Influential human ecologists have long warned of cereals' pervasive influence that links population and disease explosions in a series of plagues.^{237–243}

Pellagra Yet Cereal Reliance

On the plus side, fertility goddesses, creation myths, and harvest festivals are linked with cereals, perhaps explaining cereals' real attraction in encouraging fertility (as does their fermented derivative, alcohol). Meat, however, remains a common aversion when pregnant and is thought to have its adverse effects via the immune system. Later came pastoralism, and with it monotheistic 'Big Gods' with (almighty) shepherds and dominion over the animal kingdom, suggesting that attitudes changed in favour of a more balanced diet perhaps once the initial fertility crisis was over. Here, we may have the explanation of why plants became popular despite the costs^{244–252} (Figure 6).

Second: Co-evolution of Plant (and Later Animal) Domestication

Selective gathering and plant exploitation harnessed both their sexual and asexual reproduction. Gardening developed with

tending, weeding, pruning, and burning and then selection of phenotypic traits, availability, growth, resistance, productivity, and ease of processing or in a word nutritional yield.²⁵³ Horticulture, agriculture, and domestication of cereals and later animals are an example of convergent evolution as they happened independently and fairly quickly in different parts of the old world (later in the New World) at cultural and genetic levels, enabling better crops and digestion of starches, lactose, and meat.^{254–258} Cooking was important as it reduces toxicity of cyanogens in tuberous plants – and in the case of nicotinamide, cooking meat by roasting or boiling helps availability and cooking maize with alkali also increases bioavailability (but the practice was not always imported) as can fermentation by yeasts and germination of foods.²⁵⁹

The evolution of Village life around hearths and Quorn stones, mutual understanding and allo-parenting with sexual division of labour (it takes a village to raise a child) can be seen as enabling a descent down the food chain and increasing fertility. Subsequent horticulture-based populations, such as the Incan or the Songhay empires, were an order of magnitude lower than the cereal-based Roman or Chinese empires, and hunters have lower fertility than those on a more plant-based diet. The Agricultural revolution happened at a time of affluence, and some theoretical advantages such as storage guarding against fluctuations in climate look dubious given frequent crop failures and raids or pests attacking granaries. Farming was hard work with less leisure and many disadvantages for health other than perhaps a reduction in trauma from hunting, but overall may also have increased given intergroup warfare over meat-related resources. Evidence for poor health comes from bone and tooth pathology and is attributed to little

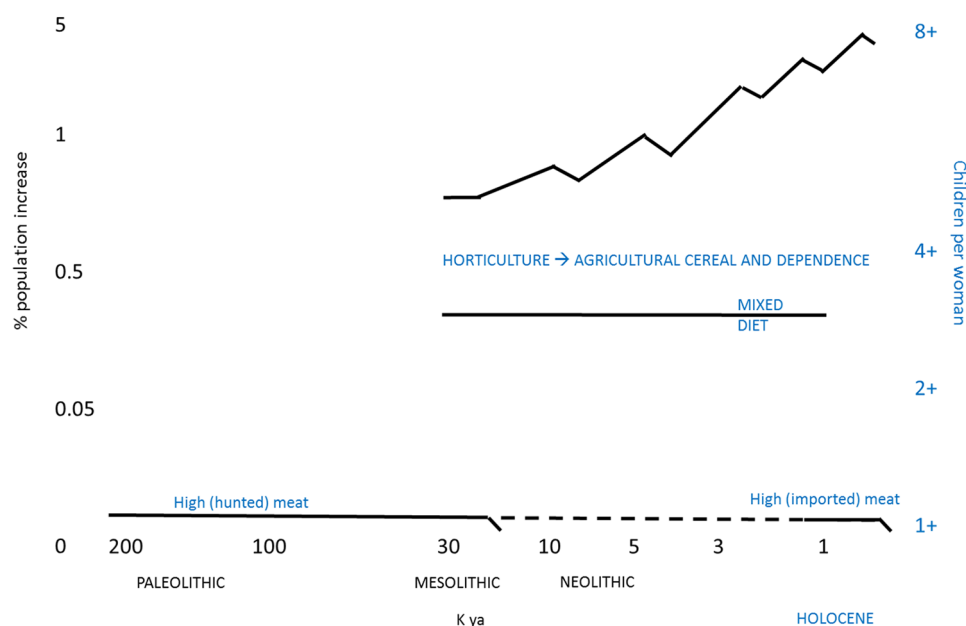


Figure 6. Original population bust 30 to 50 kya was on high meat diet and nearly caused our extinction. Neolithic and later booms were cereal dependent with busts triggered by harvest failures, poor constitution leading to plagues or wars over the meat supply. 'Goldilocks' mixed diets are the sustainable solution.

animal protein and micronutrient deficiency, including pellagra.^{260–267}

The obsessive interest with death, ancestors, deliberate burial with valuable supplies, and the after-life suggests much interest in life history and the need to procreate. Matriarchal societies may have been common reflecting that women bear the main costs of reproduction. Women may have driven both the need and best use of plant resources. Neanderthals (discussed later) could change to a more plant-based diet as fall-back foods and self-medication with similar cultural starts but with little signs of active gardening, and they may not have moved fast enough to the best sites.

Such sites enabled niche construction using stands of grasses and (tuber) plots leading to early population increases. Plant-based diets included hazelnuts, chestnuts, and acorns. Later came 'domus' settlements with gardens, then hydraulic systems, pottery, grinding stones, and cooking. Some used shellfish and other seafood rather than terrestrial meat, although fishing later declined, even in coastal areas, contributing to lower meat consumption. The pull towards plants is clear with much microlithic technology being for plant processing and use of vegetation for manufacture of textiles, cordery, dwellings, and basketry as part of the new culture. These old world data are replicated in the New World where hunter populations settled to horticulture and fishing and only then agriculture.^{262,268–278} However, the driving force for domestication has never really been explained and must be strong as it evolved independently yet diffusely in heterogeneous societies in interactive mosaics.^{279–281}

'r-selection' – Population Size Matters

Evolutionary theory has not been applied in the form of a discussion over whether the Neolithic agricultural revolution led

to 'r-selection' for quantity over 'K' selection for quality.^{282–285} Formerly favoured reasons involve a response to, rather than the cause of, population pressure despite much evidence to the contrary as populations were, in fact, low with no sign of consistent food shortages. Other species can opt for quantity or quality depending on environmental context.^{104,105,108,286–290} We argue that a lower nicotinamide dose increases immune tolerance of the foetus and fertility and that is why the move to a higher plant diet was a survival mechanism (Figure 5). The tools that we developed reflected 'r' selection with sickles, scythes, and grinding stones. This also explains why we moved further down the biodiversity and food chain to the restricted number that we domesticated as these cereals, particularly maize, are of even lower tryptophan/nicotinamide value than garden plants. The rise of Bronze and Iron Age populations may have been driven by further 'r' selected tools whether ploughs, metal scythes, and flails, axes to fell trees or cauldrons for cooking. Our environment can be intrinsically 'inadequate' in nicotinamide, but this may have been 'on purpose', leading to a decline in individual human capital but an increase in human numbers. Cereals that became staples, such as maize and rice, may have started off as luxury items, but then became linked with remarkably convergent creation and fertility myths.^{291,292}

Reproductive Control of Domesticates and Ourselves

Many have considered the Neolithic in terms of controlling reproduction of domesticates rather than ourselves, other than suggesting that sedentism with less need to transport children or more calories allowed women to have more children. We suggest that the change in diet increased fertility through this low nicotinamide biochemical-immunologic mechanism (Figure 7). Small increases in biological fertility compounded

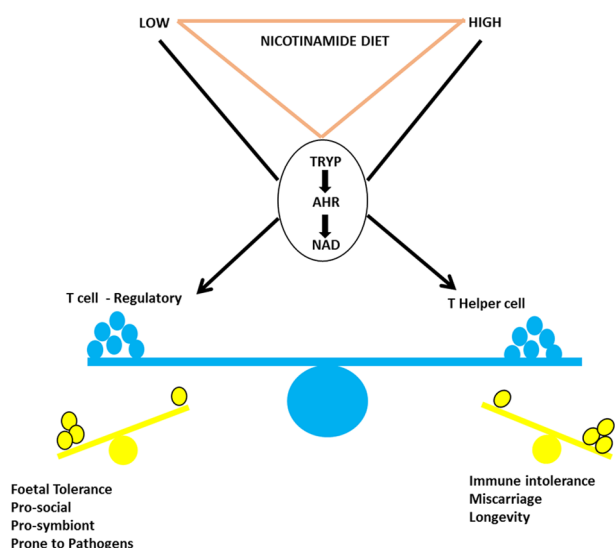


Figure 7. The nicotinamide switch: higher doses, we speculate, switch off the 'de novo' tryptophan to NAD pathway increasing a bias to immune intolerance with consequences for diseases and fertility. NAD indicates nicotinamide adenine dinucleotide.

over thousands of years lead to very different trajectories. The fundamental question is why did cultures change their mode of subsistence? The clue, we feel, is that these events are all linked with nicotinamide metabolism – pellagra being the archetypal 'disease of agriculture' and maize being the archetypal crop of 'ecological imperialism' and population explosions.

High Meat: Low Fertility

Low fertility on luxurious high meat diets was noted in ancient folklore and was a theory in preindustrial prefamily planning societies with documented correlations within countries and across the globe. Correlations of low fertility and high meat were subsequently noted in hunter-gatherers.^{125,293–295} Natural regulation of other animal populations has intrinsic controls, not reliant on starvation or predation, even if the mechanism is unknown. Human population growth may depend on the balance between cereals and meat – get this wrong and subgroups flirt with degeneration or extinction. Recent evidence, whether from genetic, cemetery skeletal, or radiocarbon data, suggests very small early populations that we emerged from before the advent of horticulture. Sustained increases can be surprisingly modest with slight changes in fertility, linked with survival, decreasing doubling of populations from thousands to hundreds of years (Figure 6). Despite earlier suggestions that sedentism increased fertility, there is little support from recent studies. Contemporary accounts of reduced fertility in affluent populations in men as well as women may also have a dietary rather than toxic explanation.

An Archaic Fertility Crisis Triggered the Dawn of Civilisation?

The common belief that the Neolithic agricultural revolution was a mistake with cultural evolution being at odds with

biological evolution is unlikely given the speed at which it was adopted at independent sites – and that agriculturalists out-produced hunter-gatherers, even if it came at a price. The price included hard work, deteriorating health and height, and even brain size with retrenchment on symbolic skills and language; even the spiritual connection with nature gained during the Mesolithic, as the first signs of scientific thought with shamans as 'ecological brokers', whether of natural history of flora and fauna or of astronomy may have reversed.^{296–299} These events all date to around 40 000 years in Europe and a population bottleneck that has been attributed to volcanic catastrophe followed by a beneficial neurological mutation, although no such thing has ever been identified. A similar scenario may have unfolded in Southern Africa much earlier also involving a population bottleneck, an adverse climate, and a move to a broader but more reliable coastal diet.^{300–304} We think it is plausible that a high level of carnivory was involved, adversely affecting fertility that we solved in different geographies and time-frames through a combination of dietary and cultural approaches leading to behavioural modernity.

Sex, Conception, and Care Obsessions Underpin Creative Explosions

We propose that a fertility crisis occurred that was solved by initially a broad-based then a lower biodiversity dietary response with progressive lowering of nicotinamide intakes. A parallel profertility and promoting culture is suggested by 'Gravettian Venuses' as fertility symbols and body ornamentation ('Venus-wear') and even the dawn of conversational languages and stories.³⁰⁵ Hunting and incipient domestication was, for a while, illustrated in cave drawings combining meat quests with sexual symbolism.^{306–342} Such art was only made over a few thousand years and miles; the obesity often depicted reflecting or perhaps advertising the reproductive advantages of a high carbohydrate diet.^{343–346} The first musical instruments, flutes, and rituals involving psychedelics and alcohol encouraging social and sexual interactions simultaneously evolved. Our conscious and emotional minds became weighted towards mating and child-care and, as long as reproduction and food were catered for, a wide variety of cultural and religious responses that could all work.^{347–353}

Climate at the time of the Last Glacial Maximum 27 000 years ago triggering flora and fauna change contributed by forcing dietary experimentation after the golden age of big game hunting and Megafaunal extinctions in a restructuring of the food web. 'Over-kill' and 'Over-chill' may both be implicated in the now seasonal and more plant-based food web. Caves and settlements were super-sites often by seashores (expanded by record low sea levels) or rivers and woods with varied ecologies and formed interconnected networks extending social reach and choice of both cultures and partners.^{278,339,354–361} Sexual selection for a mating brain perhaps took over from selection for survival. Matriarchal societies and goddesses (in a controversial literature confused with feminist

debates) may have even begun before the connection between coitus and births was recognised. The first constructed settlements were temples, not houses, used for meeting, mating, feasting, and worship of fertility gods. Female depictions concentrated on reproductive apparatus. Later, the fertility goddesses, Ceres, and many equivalents across the world, represented cereals, rites of passage, and women commonly of the plebeian and more fertile class.^{362–366}

The Mesolithic has emerged as a crucial pre-adaptation to the Neolithic. Unexploited plant and small animal/shellfish were used with multistep collecting, storage, and processing using grinding and pounding stones as their technocomplex, producing flours from both oats and underground plant storage organs as part of a behavioural package. Higher fertility overcame the localised extinctions, preceded by contractions in to refugia particularly in areas where biodiversity was low, that could have heralded the complete extinction of *Homo sapiens*, as happened to other hominins.^{115,367–375}

Fate of the Neanderthals Add to the Argument

Population implosions extinguished the Neanderthals (and Denisovans) nearly led to our demise (perhaps as low as 600–10 000 breeding pairs worldwide at times); but in the eventuality we somehow demographically and genetically swamped all other hominids. The near simultaneous timing of their demise and our creative and population explosion would be an extraordinary coincidence favouring a common mechanism. The Neanderthals were successful, outside the tropics, but were always ‘thin on the ground’, suggesting a fertility constraint also making cumulative cultural development more difficult. Their population mini-explosions have been linked with climate changes that allowed for more plants though still low by our standards (5%–30% of caloric intake) and did not stop them developing meat-related hypervitaminosis A. Interbreeding with *Homo* suggests high fertility drives, but this became their genes, but not their individual, mechanism for survival as their diet and cultural change were, as it turned out we say, not radical enough.^{262,276,376–397}

Critical Masses: ‘Foecunda virorum/Paupertas fugitur’

Population increases and sedentism encouraged division of labour and social stratification based on meat elites. Meat elites drove innovation and controlled power over the more fertile classes in a fragile social contract. The rich elite was an intellectual force, not a primate dominance structure: meat was not another material good to show off, but a need, not just a want – just as a lack of meat enabled a more fertile and labour class (who even may appreciate their children more).^{398–401} Observations that ‘proles’ (by definition) out-reproduced the rich go back to at least Roman times in writings by Pliny and laws by Augustus entreating the rich to produce more children.^{402–404}

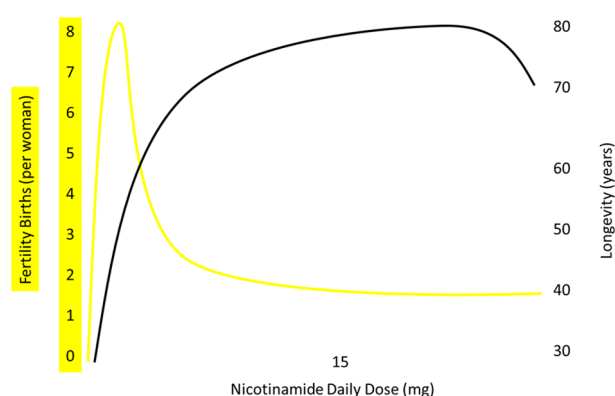


Figure 8. Dose of nicotinamide, above a minimal starvation level, we propose, negatively correlates with fertility but positively with longevity up to a point. Variable times to changing average doses, largely dependent on the meat supply, is responsible for the degree of any population boom. As the dose falls as in the Neolithic fertility rises followed by a delay then a rise in the death rate. As the dose rises, as in recent transitions, death rates fall followed after a variable delay by fertility.

Insight has been poor with intellectuals often deriding the proletarian masses let alone being the breeding ground for eugenics and other forms of class warfare, including opposing rather than appeasing revolts by the poor when starvation threatened. Such hierarchies are most obvious where meat was scarce such as South America and Africa, whether from lack of domesticates or cattle diseases. High population sizes with functioning classes develop and maintain new ideas and technology – Tasmania’s isolation and low population being the classic study of civilisations moving backward.^{405–408} Fecund agriculturalists and their cultures prevailed. Such cultures included writing that aided cereal collection, taxing, and trading. Writing may have been triggered partly by poorer memory even as higher collective intelligence overcame some loss of individual skills. Agriculturalist languages in general are intimately linked with specific cereals. Arithmetic and trading meat for cereals is the basis of many ethnic groups and plural societies: the main surviving Indo-European languages were pastoralist inventions. Even a modern metropolis, such as Chicago, was founded on grain and meat markets and good physical communications – so little has changed with the recipe for our success.^{409–411}

Demographic Transitions Spawn Civilisation

Demographically speaking, the gap as diets descend the trophic food chain between fertility rising and disease rising later (a mirror image when diets ascend) is critical to population explosions – we argue that these demographic patterns relate to the slope and direction of the meat/nicotinamide dose.^{412–422} (Figure 8).

Hygiene or Diet?

The interlinked epidemiological transition and ‘Hygiene’ hypothesis though much modified has enduring confirmation that it is important in understanding disease transitions from

infections such as TB to allergies.^{423–433} However, a convincing metabolic explanation has not been developed. The tryptophan/IDO pathway and links to TB that excretes nicotinic acid may be key to this puzzle for these transitions (reversed at times such as war when increases in TB coincide with drops in allergy).^{434–436} The symbiont microbiome (rather than childhood acute infection) and the key involvement of Tregs mediated by tryptophan metabolism in the switch to auto-immune disease are likely players^{422,437–441} (Figure 5). Undernutrition, after all, is the commonest cause of immune-deficiency relevant to many infections, including TB with nicotinamide having anti-microbial activity against many classes of chronic infections; and overnutrition may be the driver and intersection for dysbioses and immune intolerance affecting Tregs interacting with metabolic, energy, and amino-acid sensors.^{442–462}

Conclusions

The ‘Chinese Malthus’ Hong Liangji (1793) noted high fertility on the American import, maize. In retrospect, all population explosions and increases in biological ‘fitness’ (even as health deteriorated) were probably caused by a move down the food chain. Many original hunter-gatherer populations may have ‘tottered’, and to prosper the (more fertile) egg needed to come first. Sowed cereals and agriculture were not ‘invented’ because of population pressures, as there was no pressure, but the exact opposite of relative infertility. Now, we are reaping the downside as some populations, such as in Africa, continue to boom but will bust, or exacerbate climate change, but if the pendulum swings too far towards meat infertile populations, such as many in Europe, become equally problematic for healthy economics and the need for migration.^{463–481}

Meat originally drove brain evolution and survival, but at the price of low fertility. The move to more plants and then more cereals solved low biological fertility by steadily increasing immune tolerance of the foetus. This came with profertility cultures influencing our unusual life history and the way people farmed, mated, cooked, recorded, interacted, bonded, and believed.^{442,482,483} The ‘sapient paradox’ of the delay before behavioural modernity explained by the need get the dietary, life-history, and social base, along with genetic modifications, to drive multifaceted profertility cultures in a concerted evolutionary approach with exponential consequences that shape the modern world.^{484–489}

Our genome includes profertility genes dating from this time. These genetic signatures are as close as we are likely to get to proof that an early fertility crisis drove our dietary, nutrigenomic, and cultural evolution.^{490–492} Such genes now show up as examples of ‘antagonistic pleiotropy’ aiding fertility and growth early in life, but later are risk factors for cancer and neurodegeneration. Alongside preventing extremes in nicotinamide dosage and boosting the dose at times of stress, these trade-offs may be preventable by personalising nicotinamide dose depending on genomic and environmen-

tal background, and age-arguments we develop in our companion article.^{394,493–501}

Author Contributions

AW and LJH drafted, proofed and submitted the final manuscript.

ORCID iD

Lisa J Hill  <https://orcid.org/0000-0001-8431-7029>

REFERENCES

- Gosden C, Hather JG. *The Prehistory of Food: Appetites for Change*. Abingdon, UK: Routledge; 2004.
- Cohen MN. *The Food Crisis in Prehistory: Overpopulation and the Origins of Agriculture*. New Haven, CT: Yale University Press; 1977.
- de Secondat baron de Montesquieu C, Cohler AM, Miller BC, Stone HS. *Montesquieu: The Spirit of the Laws*. Cambridge, UK: Cambridge University Press; 1989.
- McNeill WH. *The Rise of the West: A History of the Human Community*. Chicago, IL: University of Chicago Press; 1992.
- Clark G. *A Farewell to Alms: A Brief Economic History of the World*. Princeton, NJ: Princeton University Press; 2008.
- Crosby AW. *Ecological Imperialism: The Biological Expansion of Europe, 900–1900*. Cambridge, UK: Cambridge University Press; 1993.
- Diamond JM. *Guns, Germs, and Steel: The Fates of Human Societies*. New York, NY: W.W. Norton; 1999.
- Childe VG. *Man Makes Himself*. London, England: Watts; 1936.
- Romer PM. The origins of endogenous growth. *J Econ Perspect*. 1994;8:3–22.
- Citarella M, Teotia S, Lamb RS. Evolutionary history of the poly (ADP-ribose) polymerase gene family in eukaryotes. *BMC Evol Biol*. 2010;10:308.
- Lunzer M, Miller SP, Felsheim R, Dean AM. The biochemical architecture of an ancient adaptive landscape. *Science*. 2005;310:499–501.
- Ternes CM, Schonknecht G. Gene transfers shaped the evolution of de novo NAD⁺ biosynthesis in eukaryotes. *Genome Biol Evol*. 2014;6:2335–2349.
- Zhu G, Golding GB, Dean AM. The selective cause of an ancient adaptation. *Science*. 2005;307:1279–1282.
- Lane N. *Life Ascending: The Ten Great Inventions of Evolution*. London, England: Profile; 2010.
- Elhassan YS, Philp AA, Lavery GG. Targeting NAD⁺ in metabolic disease; new insights into an old molecule. *J Endocr Soc*. 2017;1:816–835.
- Belenky P, Racette FG, Bogan KL, McClure JM, Smith JS, Brenner C. Nicotinamide riboside promotes Sir2 silencing and extends lifespan via Nrk and Urh1/Pnp1/Meu1 pathways to NAD⁺. *Cell*. 2007;129:473–484.
- Makarov MV, Trammell SAJ, Migaud ME. The chemistry of the vitamin B3 metabolome. *Biochem Soc Trans*. 2019;47:131–147.
- Kulikova VA, Gromyko DV, Nikiforov AA. The regulatory role of NAD in human and animal cells. *Biochemistry (Mosc)*. 2018;83:800–812.
- Jacobson MK, Jacobson EL. Vitamin B3 in health and disease: toward the second century of discovery. *Methods Mol Biol*. 2018;1813:3–8.
- Huntington E. *Mainsprings of Civilization*. New York, NY: New American Library/Mentor Books; 1959.
- Fernandez-Armesto F. *Civilizations: Culture, Ambition, and the Transformation of Nature*. New York, NY: Free Press; 2001.
- DeCasien AR, Williams SA, Higham JP. Primate brain size is predicted by diet but not sociality. *Nat Ecol Evol*. 2017;1:112.
- McNeill JR, Engelke P. *The Great Acceleration*. Cambridge, MA: Harvard University Press; 2016.
- Barker G, Goucher C. *The Cambridge World History: Volume 2, a World with Agriculture, 12,000 BCE–500 CE*. Cambridge, UK: Cambridge University Press; 2015.
- Clark G. *Mesolithic Prelude: The Palaeolithic-Neolithic Transition in Old World Prehistory*. Edinburgh, UK: Edinburgh University Press; 1980.
- Rosas A, Ríos L, Estalrich A, et al. The growth pattern of Neandertals, reconstructed from a juvenile skeleton from El Sidrón (Spain). *Science*. 2017;357:1282–1287.
- Cohen MN, Armelagos GJ, Larsen CS. *Paleopathology at the Origins of Agriculture*. Gainesville, FL: University Press of Florida; 2013.
- Armelagos GJ, Harper KN. Genomics at the origins of agriculture, part two. *Evol Anthropol*. 2005;14:109–121.
- Kiple KF. *A Movable Feast: Ten Millennia of Food Globalization*. Cambridge, UK: Cambridge University Press; 2007.
- Lenski G. *Ecological-Evolutionary Theory: Principles and Applications*. Boulder, CO: Paradigm Publishers; 2005.

31. Brüssow H. *The Quest for Food: A Natural History of Eating*. New York, NY: Springer; 2007.
32. Pasternak CA. *Quest: The Essence of Humanity*. Hoboken, NJ: Wiley; 2003.
33. Gillis RE, Kovačiková L, Bréhard S, et al. The evolution of dual meat and milk cattle husbandry in Linearbandkeramik societies. *Proc Biol Sci*. 2017;284:20170905.
34. Kelly RL. *The Foraging Spectrum*. Washington, DC: Smithsonian Institution Press; 1995.
35. Nettle D. Language and genes: a new perspective on the origins of human cultural diversity. *Proc Natl Acad Sci U S A*. 2007;104:10755–10756.
36. Allen JS. *The Omnivorous Mind: Our Evolving Relationship with Food*. Cambridge, MA: Harvard University Press; 2012.
37. Cerulli T. *The Mindful Carnivore: A Vegetarian's Hunt for Sustenance*. New York, NY: Pegasus Books; 2013.
38. Crowe I. *The Quest for Food: Its Role in Human Evolution & Migration*. Stroud, UK: Tempus Pub Limited; 2000.
39. Dwyer PD. The price of protein: five hundred hours of hunting in the New Guinea highlands. *Oceania*. 1974;44:278–293.
40. Dwyer PD. Choice and constraint in a Papua New Guinean food quest. *Hum Ecol*. 1985;13:49–70.
41. Eaton SB, Konner MJ, Cordain L. *Diet-Dependent Acid Load, Paleolithic Nutrition, and Evolutionary Health Promotion*. Oxford, UK: Oxford University Press; 2009.
42. Etkin NL. *Eating on the Wild Side: The Pharmacologic, Ecologic and Social Implications of Using Noncultigens*. Tucson, AZ: University of Arizona Press; 2000.
43. Gamble C. *Timewalkers: The Prehistory of Global Colonization*. Cambridge, MA: Harvard University Press; 1994.
44. Goodall J, Berman P. *Reason for Hope: A Spiritual Journey*. New York, NY: Grand Central Publishing; 1999.
45. Hardy K, Brand-Miller J, Brown KD, Thomas MG, Copeland L. The importance of dietary carbohydrate in human evolution. *Q Rev Biol*. 2015;90:251–268.
46. Harris DR, Hillman GC. *Foraging and Farming: The Evolution of Plant Exploitation*. Abingdon, UK: Routledge; 2014.
47. Hill K. Macronutrient modifications of optimal foraging theory: an approach using indifference curves applied to some modern foragers. *Hum Ecol*. 1988;16:157–197.
48. Hobhouse H. *Seeds of Change: Five Plants That Transformed Mankind*. New York, NY: Perennial Library; 1987.
49. Hood B. *The Domesticated Brain: A Pelican Introduction*. London, England: Penguin Books; 2014.
50. Johns T. *With Bitter Herbs They Shall Eat It: Chemical Ecology and the Origins of Human Diet and Medicine*. Tucson, AZ: University of Arizona Press; 1990.
51. Kuhn SL, Stiner MC. The antiquity of hunter-gatherers. In: Panter-Brick C, Layton RH, Rowley-Conwy PA, eds. *Another Day, Another Camp: An Interdisciplinary View of Hunter-gatherers*. Cambridge, UK: Cambridge University Press; 2001:99–142.
52. Laland KN. *Darwin's Unfinished Symphony: How Culture Made the Human Mind*. Princeton, NJ: Princeton University Press; 2018.
53. Meltzer DJ. *First Peoples in a New World: Colonizing Ice Age America*. Berkeley, CA: University of California Press; 2009.
54. Milton K. Ecological foundations for subsistence strategies among the Mbuti Pygmies. *Hum Ecol*. 1985;13:71–78.
55. Rindos D. *The Origins of Agriculture: An Evolutionary Perspective*. Amsterdam, The Netherlands: Elsevier Science; 2013.
56. Shyock A, Smail DL, Earle T, Feeley-Harnik G. *Deep History: The Architecture of Past and Present*. Berkeley, CA: University of California Press; 2012.
57. Smail DL. *On Deep History and the Brain*. Berkeley, CA: University of California Press; 2008.
58. Tudge C. *Neanderthals, Bandits and Farmers: How Agriculture Really Began*. New Haven, CT: Yale University Press; 1999.
59. Wells S. *Pandora's Seed: The Unforeseen Cost of Civilization*. London, England: Penguin Books; 2010.
60. Bellwood P. *First Farmers: The Origins of Agricultural Societies*. Hoboken, NJ: Wiley; 2004.
61. Price TD. *Europe's First Farmers*. Cambridge, UK: Cambridge University Press; 2000.
62. Dyble M, Thompson J, Smith D, et al. Networks of food sharing reveal the functional significance of multilevel sociality in two hunter-gatherer groups. *Curr Biol*. 2016;26:2017–2021.
63. Mace R. Evolutionary ecology of human life history. *Anim Behav*. 2000;59:1–10.
64. Sauer CO. *Agricultural Origins and Dispersals – Primary Source Edition*. Charleston, SC: BiblioLife; 2014.
65. Barton H, Denham T. Vegetables and the social-biological transformations of plants and people. *Quatern Int*. 2018;489:17–25.
66. Brown TA. The role of humans in a protracted transition from hunting-gathering to plant domestication in the Fertile Crescent. *Front Plant Sci*. 2018;9:1287.
67. Lefebvre L, Reader SM, Sol D. Brains, innovations and evolution in birds and primates. *Brain Behav Evol*. 2004;63:233–246.
68. Ofek H. *Second Nature: Economic Origins of Human Evolution*. Cambridge, UK: Cambridge University Press; 2001.
69. Attanasio O, Mesnard A. The impact of a conditional cash transfer programme on consumption in Colombia. *Fisc Stud*. 2006;27:421–442.
70. Hulme D, Joseph Hanlon ABDH, Hanlon J, Barrientos A. *Just Give Money to the Poor: The Development Revolution from the Global South*. Boulder, CO: Lynne Rienner Publishers; 2012.
71. Prais SJ, Houthakker HS. *The Analysis of Family Budgets*. Cambridge, UK: Cambridge University Press; 1971.
72. Steensland B. *The Failed Welfare Revolution: America's Struggle over Guaranteed Income Policy*. Princeton, NJ: Princeton University Press; 2011.
73. Szreter S. The idea of demographic transition and the study of fertility change: a critical intellectual history. *Popul Dev Rev*. 1993;19:659–701.
74. Cox CB, Moore PD, Ladle R. *Biogeography: An Ecological and Evolutionary Approach*. Hoboken, NJ: Wiley; 2016.
75. Burroughs WJ. *Climate Change in Prehistory: The End of the Reign of Chaos*. Cambridge, UK: Cambridge University Press; 2005.
76. Demenocal PB. African climate change and faunal evolution during the Pliocene–Pleistocene. *Earth Planet Sc Lett*. 2004;220:3–24.
77. King G, Bailey G. Tectonics and human evolution. *Antiquity*. 2006;80:265–286.
78. Maslin MA, Christensen B. Tectonics, orbital forcing, global climate change, and human evolution in Africa: introduction to the African paleoclimate special volume. *J Hum Evol*. 2007;53:443–464.
79. Sepulchre P, Ramstein G, Fluteau F, Schuster M, Tiercelin J-J, Brunet M. Tectonic uplift and Eastern Africa aridification. *Science*. 2006;313:1419–1423.
80. Grine FE. *Evolutionary History of the Robust Australopithecines*. Abingdon, UK: Routledge; 2017.
81. Cartmill M. *A View to a Death in the Morning: Hunting and Nature through History*. Cambridge, MA: Harvard University Press; 2009.
82. Martin PS, Wright HE. *Pleistocene Extinctions: The Search for a Cause*. New Haven, CT: Yale University Press; 1967.
83. Panter-Brick C, Layton RH, Rowley-Conwy P. *Hunter-Gatherers: An Interdisciplinary Perspective*. Cambridge, UK: Cambridge University Press; 2001.
84. Trauth MH, Larrasoana JC, Mudelsee M. Trends, rhythms and events in Plio-Pleistocene African climate. *Quaternary Sci Rev*. 2009;28:399–411.
85. Pickering T. *Rough and Tumble: Aggression, Hunting, and Human Evolution*. Berkeley, CA: University of California Press; 2013.
86. Lee RB, DeVore I. *Man the Hunter*. New York, NY: Routledge; 2017.
87. Speth JD, Spielmann KA. Energy source, protein metabolism, and hunter-gatherer subsistence strategies. *J Anthropol Archaeol*. 1983;2:1–31.
88. Bellwood P, Oxenham M. The expansions of farming societies and the role of the neolithic demographic transition. In: Bocquet-Appel J-P, Bar-Yosef O, eds. *The Neolithic Demographic Transition and its Consequences*. Dordrecht, The Netherlands: Springer; 2008:13–34.
89. Hanks LM. *Rice and Man: Agricultural Ecology in Southeast Asia*. Honolulu, HI: University of Hawaii Press; 1992.
90. Standage T. *An Edible History of Humanity*. New York, NY: Atlantic Books; 2012.
91. Allen MW, Bettinger RL, Coddling BF, Jones TL, Schwitalla AW. Resource scarcity drives lethal aggression among prehistoric hunter-gatherers in central California. *Proc Natl Acad Sci U S A*. 2016;113:12120–12125.
92. Martin PS, Klein RG. *Quaternary Extinctions: A Prehistoric Revolution*. Tucson, AZ: University of Arizona Press; 1989.
93. Turvey ST. *Holocene Extinctions*. Oxford, UK: Oxford University Press; 2009.
94. Algaze G. *Ancient Mesopotamia at the Dawn of Civilization: The Evolution of an Urban Landscape*. Chicago, IL: University of Chicago Press; 2009.
95. Postgate N. *Early Mesopotamia: Society and Economy at the Dawn of History*. Abingdon, UK: Routledge; 2017.
96. Staller J, Carrasco M. *Pre-Columbian Foodways: Interdisciplinary Approaches to Food, Culture, and Markets in Ancient Mesoamerica*. New York, NY: Springer; 2009.
97. Aufderheide AC, Rodríguez-Martín C. *The Cambridge Encyclopedia of Human Paleopathology*. Cambridge, UK: Cambridge University Press; 1998.
98. Waldron T. *Palaeopathology*. Cambridge, UK: Cambridge University Press; 2008.
99. Gregg SA. *Foragers and Farmers: Population Interaction and Agricultural Expansion in Prehistoric Europe*. Chicago, IL: University of Chicago Press; 1988.
100. Handwerker WP. The first demographic transition: an analysis of subsistence choices and reproductive consequences. *Am Anthropol*. 1983;85:5–27.
101. Hill K, Kaplan H. Tradeoffs in male and female reproductive strategies among the Ache: part 1. In: Mulder MB, Betzig LL, Turke P, eds. *Human Reproductive Behavior: A Darwinian Perspective*. Cambridge, UK: Cambridge University Press; 1988:277–290.
102. Shennan S. Demography and cultural innovation: a model and its implications for the emergence of modern human culture. *Camb Archaeol J*. 2001;11:5–16.

103. Ammerman AJ, Cavalli-Sforza LL. *The Neolithic Transition and the Genetics of Populations in Europe*. Princeton, NJ: Princeton University Press; 2014.
104. Borgerhoff Mulder M. Optimizing offspring: the quantity-quality tradeoff in agropastoral Kipsigis. *Evol Hum Behav*. 2000;21:391–410.
105. Gillespie DO, Russell AF, Lummaa V. When fecundity does not equal fitness: evidence of an offspring quantity versus quality trade-off in pre-industrial humans. *Proc Biol Sci*. 2008;275:713–722.
106. Hassett B. *Built on Bones: 15,000 Years of Urban Life and Death*. London, England: Bloomsbury Publishing; 2017.
107. Pinhasi R, Stock JT. *Human Bioarchaeology of the Transition to Agriculture*. Hoboken, NJ: Wiley; 2011.
108. Lambert PM. Health versus fitness: competing themes in the origins and spread of agriculture? *Curr Anthropol*. 2009;50:603–608.
109. Lawson DW, Alvergne A, Gibson MA. The life-history trade-off between fertility and child survival. *Proc Biol Sci*. 2012;279:4755–4764.
110. Wenke RJ. *Patterns in Prehistory: Humankind's First Three Million Years*. Oxford, UK: Oxford University Press; 1999.
111. Bocquet-Appel J-P. When the world's population took off: the springboard of the Neolithic Demographic Transition. *Science*. 2011;333:560–561.
112. Cohen MN. Introduction: rethinking the origins of agriculture. *Curr Anthropol*. 2009;50:591–595.
113. Eshed V, Gopher A, Gage TB, HersHKovitz I. Has the transition to agriculture reshaped the demographic structure of prehistoric populations? New evidence from the Levant. *Am J Phys Anthropol*. 2004;124:315–329.
114. Gignoux CR, Henn BM, Mountain JL. Rapid, global demographic expansions after the origins of agriculture. *Proc Natl Acad Sci U S A*. 2011;108:6044–6049.
115. Shennan S, Downey SS, Timpson A, et al. Regional population collapse followed initial agriculture booms in mid-Holocene Europe. *Nat Commun*. 2013;4:2486.
116. Warden L, Moros M, Neumann T, et al. Climate induced human demographic and cultural change in northern Europe during the mid-Holocene. *Sci Rep*. 2017;7:15251.
117. Zahid HJ, Robinson E, Kelly RL. Agriculture, population growth, and statistical analysis of the radiocarbon record. *Proc Natl Acad Sci U S A*. 2016;113:931–935.
118. Zheng H-X, Yan S, Qin Z-D, Jin L. MtDNA analysis of global populations support that major population expansions began before Neolithic Time. *Sci Rep*. 2012;2:745.
119. Bailey G, Spikins P. *Mesolithic Europe*. Cambridge, UK: Cambridge University Press; 2008.
120. Divale WT. Migration, external warfare, and matrilineal residence. *Behav Sci Res*. 1974;9:75–133.
121. Sahlins MD. *Stone Age Economics*. Chicago, IL: Aldine; 1972.
122. Sahlins M. The original affluent society. In: Gowdy J. ed. *Limited Wants, Unlimited Means: A Reader on Hunter-Gatherer Economics and the Environment*. Washington, DC: Island Press; 1998:5–41.
123. Seddon C. *Humans: From the Beginning: From the First Apes to the First Cities*. Cambridge, UK: Glanville Publications; 2015.
124. Oppenheimer S. *The Real Eve: Modern Man's Journey Out of Africa*. New York, NY: Carroll & Graf; 2003.
125. Bevan A, Colledge S, Fuller D, Fyfe R, Shennan S, Stevens C. Holocene fluctuations in human population demonstrate repeated links to food production and climate. *Proc Natl Acad Sci U S A*. 2017;114:E10524–E10531.
126. Boserup E. *Population and Technological Change: A Study of Long-Term Trends*. Chicago, IL: University of Chicago Press; 1983.
127. Downey SS, Haas WR Jr, Shennan SJ. European Neolithic societies showed early warning signals of population collapse. *Proc Natl Acad Sci U S A*. 2016;113:9751–9756.
128. Page AE, Chaudhary N, Viguiet S, et al. Hunter-gatherer social networks and reproductive success. *Sci Rep*. 2017;7:1153.
129. Stefansson V. *Not by Bread Alone*. New York, NY: Macmillan; 1946.
130. Johnston BF, Mellor JW. The role of agriculture in economic development. *Am Econ Rev*. 1961;51:566–593.
131. Baez-Mendoza R, Harris CJ, Schultz W. Activity of striatal neurons reflects social action and own reward. *Proc Natl Acad Sci U S A*. 2013;110:16634–16639.
132. Bergey CM, Phillips-Conroy JE, Disotell TR, Jolly CJ. Dopamine pathway is highly diverged in primate species that differ markedly in social behavior. *Proc Natl Acad Sci U S A*. 2016;113:6178–6181.
133. Brodie BB, Pletscher A, Shore PA. Evidence that serotonin has a role in brain function. *Science*. 1955;122:968.
134. Caravaggio F, Chung JK, Gerretsen P, et al. Exploring the relationship between social attachment and dopamine D2/3 receptor availability in the brains of healthy humans using [11C]-(+)-PHNO. *Soc Neurosci*. 2017;12:163–173.
135. Curtis JT, Liu Y, Aragona BJ, Wang Z. Dopamine and monogamy. *Brain Res*. 2006;1126:76–90.
136. Edsinger E, Dolen G. A conserved role for serotonergic neurotransmission in mediating social behavior in octopus. *Curr Biol*. 2018;28:3136–3142.e4.
137. Fam BSO, Pare P, Felkl AB, et al. Oxytocin and arginine vasopressin systems in the domestication process. *Genet Mol Biol*. 2018;41:235–242.
138. Finkenwirth C, Martins E, Deschner T, Burkart JM. Oxytocin is associated with infant-care behavior and motivation in cooperatively breeding marmoset monkeys. *Horm Behav*. 2016;80:10–18.
139. Insel TR, Shapiro LE. Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. *Proc Natl Acad Sci U S A*. 1992;89:5981–5985.
140. Leyton M, Okazawa H, Diksic M, et al. Brain regional α -[11C] methyl-L-tryptophan trapping in impulsive subjects with borderline personality disorder. *Am J Psychiat*. 2001;158:775–782.
141. Lovejoy CO. Reexamining human origins in light of *Ardipithecus ramidus*. *Science*. 2009;326:74–74e8.
142. Matsui S, Sasaki T, Kohno D, et al. Neuronal SIRT1 regulates macronutrient-based diet selection through FGF21 and oxytocin signalling in mice. *Nat Commun*. 2018;9:4604.
143. Passamonti L, Crockett MJ, Apergis-Schoute AM, et al. Effects of acute tryptophan depletion on prefrontal-amygdala connectivity while viewing facial signals of aggression. *Biol Psychiatry*. 2012;71:36–43.
144. Pearce E, Wlodarski R, Machin A, Dunbar RI. Variation in the β -endorphin, oxytocin, and dopamine receptor genes is associated with different dimensions of human sociality. *Proc Natl Acad Sci U S A*. 2017;114:5300–5305.
145. Rilling JK, Scholz J, Preuss TM, Glasser MF, Errangi BK, Behrens TE. Differences between chimpanzees and bonobos in neural systems supporting social cognition. *Soc Cogn Affect Neurosci*. 2012;7:369–379.
146. Robbins TW. Opinion on monoaminergic contributions to traits and temperament. *Philos Trans R Soc Lond B Biol Sci*. 2018;373:20170153.
147. Stephenson AR, Edler MK, Erwin JM, et al. Cholinergic innervation of the basal ganglia in humans and other anthropoid primates. *J Comp Neurol*. 2017;525:319–332.
148. Stimpson CD, Barger N, Taglialetela JP, et al. Differential serotonergic innervation of the amygdala in bonobos and chimpanzees. *Soc Cogn Affect Neurosci*. 2015;11:413–422.
149. Tanaka SC, Schweighofer N, Asahi S, et al. Serotonin differentially regulates short- and long-term prediction of rewards in the ventral and dorsal striatum. *PLoS ONE*. 2007;2:e1333.
150. van de Giessen E, Rosell DR, Thompson JL, et al. Serotonin transporter availability in impulsive aggressive personality disordered patients: a PET study with [11C] DASB. *J Psychiat Res*. 2014;58:147–154.
151. Wrangham R. *The Goodness Paradox: How Evolution Made Us Both More and Less Violent*. London, England: Profile; 2019.
152. Young LJ, Wang Z. The neurobiology of pair bonding. *Nat Neurosci*. 2004;7:1048.
153. Zhong J, Amina S, Liang M, et al. Cyclic ADP-ribose and heat regulate oxytocin release via CD38 and TRPM2 in the hypothalamus during social or psychological stress in mice. *Front Neurosci*. 2016;10:304.
154. Bonhommeau S, Dubroca L, Le Pape O, et al. Eating up the world's food web and the human trophic level. *Proc Natl Acad Sci U S A*. 2013;110:20617–20620.
155. Counihan C, Van Esterik P. *Food and Culture: A Reader*. New York, NY: Routledge; 2013.
156. Mead M, Textor RB. *The World Ahead: An Anthropologist Anticipates the Future*. New York, NY: Berghahn Books; 2005.
157. Nebert DW, Wikvall K, Miller WL. Human cytochromes P450 in health and disease. *Philos Trans R Soc Lond B Biol Sci*. 2013;368:20120431.
158. Gerbault P, Liebert A, Itan Y, et al. Evolution of lactase persistence: an example of human niche construction. *Philos Trans R Soc Lond B Biol Sci*. 2011;366:863–877.
159. Itan Y, Jones BL, Ingram CJ, Swallow DM, Thomas MG. A worldwide correlation of lactase persistence phenotype and genotypes. *BMC Evol Biol*. 2010;10:36.
160. Salque M, Bogucki PI, Pyzel J, et al. Earliest evidence for cheese making in the sixth millennium bc in northern Europe. *Nature*. 2012;493:522.
161. Speth JD. Seasonality, resource stress, and food sharing in so-called 'egalitarian' foraging societies. *J Anthropol Archaeol*. 1990;9:148–188.
162. Sear R, Lawson DW, Kaplan H, Shenk MK. Understanding variation in human fertility: what can we learn from evolutionary demography? *Philos Trans R Soc Lond B Biol Sci*. 2016;371:20150144.
163. Raghanti MA, Edler MK, Stephenson AR, et al. A neurochemical hypothesis for the origin of hominids. *Proc Natl Acad Sci U S A*. 2018;115:E1108–E1116.
164. Wei H, Liu S, Lian R, et al. Abnormal expression of indoleamine 2, 3-dioxygenase in human recurrent miscarriage [published online ahead of print March 4, 2019]. *Reprod Sci*. doi:10.1177/1933719119833788.
165. Mesoudi A. *Cultural Evolution: How Darwinian Theory Can Explain Human Culture and Synthesize the Social Sciences*. Chicago, IL: University of Chicago Press; 2011.
166. Roth G, Dicke U. Evolution of the brain and intelligence. *Trends Cogn Sci*. 2005;9:250–257.
167. Scarre C. *The Human Past: World Prehistory and the Development of Human Societies*. London, England: Thames & Hudson; 2005.

168. Bramble DM, Lieberman DE. Endurance running and the evolution of Homo. *Nature*. 2004;432:345.
169. Wheeler PE. The evolution of bipedality and loss of functional body hair in hominids. *J Hum Evol*. 1984;13:91–98.
170. Fogarty L, Creanza N. The niche construction of cultural complexity: interactions between innovations, population size and the environment. *Philos Trans R Soc Lond B Biol Sci*. 2017;372:20160428.
171. Butler AB. Evolution of brains, cognition, and consciousness. *Brain Res Bull*. 2008;75:442–449.
172. Donald M. *A Mind So Rare: The Evolution of Human Consciousness*. New York, NY: W.W. Norton; 2002.
173. Eccles JC. Evolution of consciousness. *Proc Natl Acad Sci U S A*. 1992;89:7320–7324.
174. Kann O, Huchzermeyer C, Kovacs R, Wirtz S, Schuelke M. Gamma oscillations in the hippocampus require high complex I gene expression and strong functional performance of mitochondria. *Brain*. 2011;134:345–358.
175. Tomasello M. *The Cultural Origins of Human Cognition*. Cambridge, MA: Harvard University Press; 2009.
176. Bowles S, Gintis H. *A Cooperative Species: Human Reciprocity and Its Evolution*. Princeton, NJ: Princeton University Press; 2011.
177. Clayton NS, Emery NJ. Avian models for human cognitive neuroscience: a proposal. *Neuron*. 2015;86:1330–1342.
178. Rosati AG. Foraging cognition: reviving the ecological intelligence hypothesis. *Trends Cogn Sci*. 2017;21:691–702.
179. Dunbar R. *Grooming, Gossip, and the Evolution of Language*. Cambridge, MA: Harvard University Press; 1998.
180. Jaynes J. *The Origin of Consciousness in the Breakdown of the Bimodal Mind*. Boston, MA: Houghton Mifflin Harcourt; 2000.
181. Plotkin H. *Evolution in Mind: An Introduction to Evolutionary Psychology*. Cambridge, MA: Harvard University Press; 1997.
182. Vigne J-D. The origins of animal domestication and husbandry: a major change in the history of humanity and the biosphere. *C R Biol*. 2011;334:171–181.
183. Clutton-Brock J. *The Walking Larder: Patterns of Domestication, Pastoralism, and Predation*. Abingdon, UK: Routledge; 2014.
184. Perren R. *The Meat Trade in Britain, 1840–1914*. London, England: Routledge and Kegan Paul; 1978.
185. Rixson D. *The History of Meat Trading*. Nottingham, UK: Nottingham University Press; 2000.
186. Avramescu C, Blyth AI. *An Intellectual History of Cannibalism*. Princeton, NJ: Princeton University Press; 2011.
187. Diehl D, Donnelly MP. *Eat Thy Neighbour: A History of Cannibalism*. Stroud, UK: History Press; 2012.
188. Turnbull C. *Mountain People*. New York, NY: Simon & Schuster; 1987.
189. de Almeida RM, Cabral JC, Narvaes R. Behavioural, hormonal and neurobiological mechanisms of aggressive behaviour in human and nonhuman primates. *Physiol Behav*. 2015;143:121–135.
190. McKeown T. *The Role of Medicine: Dream, Mirage, or Nemesis?* Princeton, NJ: Princeton University Press; 2014.
191. London D, Hruschka D. Helminths and human ancestral immune ecology: what is the evidence for high helminth loads among foragers? *Am J Hum Biol*. 2014;26:124–129.
192. Leles D, Reinhard KJ, Fugassa M, Ferreira LF, Iñiguez AM, Araújo A. A parasitological paradox: why is ascarid infection so rare in the prehistoric Americas? *J Archaeol Sci*. 2010;37:1510–1520.
193. Humphrey LT, De Groote I, Morales J, et al. Earliest evidence for caries and exploitation of starchy plant foods in Pleistocene hunter-gatherers from Morocco. *Proc Natl Acad Sci U S A*. 2014;111:954–959.
194. Hugot JP, Reinhard KJ, Gardner SL, Morand S. Human enterobiasis in evolution: origin, specificity and transmission. *Parasite*. 1999;6:201–208.
195. Hotez PJ, Bethony J, Bottazzi ME, Brooker S, Buss P. Hookworm: 'The Great Infection of Mankind'. *PLoS Med*. 2005;2:e67.
196. Hershkovitz I, Donoghue HD, Minnikin DE, et al. Detection and molecular characterization of 9,000-year-old Mycobacterium tuberculosis from a Neolithic settlement in the Eastern Mediterranean. *PLoS ONE*. 2008;3:e3426.
197. Rasmussen S, Allentoft ME, Nielsen K, et al. Early divergent strains of *Yersinia pestis* in Eurasia 5,000 years ago. *Cell*. 2015;163:571–582.
198. Baab KL. The place of *Homo floresiensis* in human evolution. *J Anthropol Sci*. 2016;94:5–18.
199. Harcourt-Smith W. Early hominin diversity and the emergence of the genus Homo. *J Anthropol Sci*. 2016;94:19–27.
200. Hawks J, Elliott M, Schmid P, et al. New fossil remains of *Homo naledi* from the Lesedi Chamber, South Africa. *eLife*. 2017;6:e24232.
201. Stringer C. Human evolution: the many mysteries of Homo naledi. *eLife*. 2015;4:e10627.
202. Perry GH, Dominy NJ. Evolution of the human pygmy phenotype. *Trends Ecol Evol*. 2009;24:218–225.
203. Cartwright FF, Biddiss MD. *Disease & History*. Stroud, UK: Sutton; 2004.
204. Dormandy T. *The White Death: A History of Tuberculosis*. New York, NY: Hambleton and London; 2002.
205. Hardy A. *Health and Medicine in Britain since 1860*. Basingstoke, UK: Palgrave; 2001.
206. Harrison M. *Disease and the Modern World: 1500 to the Present Day*. Hoboken, NJ: Wiley; 2013.
207. Hays JN. *The Burdens of Disease: Epidemics and Human Response in Western History*. New Brunswick, NJ: Rutgers University Press; 2009.
208. McNeill W. *Plagues and Peoples*. New York, NY: Knopf Doubleday Publishing Group; 2010.
209. Fussell BH. *The Story of Corn*. Albuquerque, NM: University of New Mexico Press; 1992.
210. Giles D. *Singing Valleys: The Story of Corn*. New York, NY: Random House; 1940.
211. Cockburn TA. Infectious diseases in ancient populations. *Curr Anthropol*. 1971;12:45–62.
212. Karlen A. *Plague's Progress: A Social History of Man and Disease*. London, England: Phoenix; 2001.
213. Nisbett RE. *Culture of Honor: The Psychology of Violence in the South*. New York, NY: Routledge; 2018.
214. Pick D. *Faces of Degeneration: A European Disorder, C.1848–1918*. Cambridge, UK: Cambridge University Press; 1993.
215. Berry SS. The food crisis and agrarian change in Africa: a review essay. *Afr Stud Rev*. 1984;27:59–112.
216. Blake M. *Maize for the Gods: Unearthing the 9,000-Year History of Corn*. Berkeley, CA: University of California Press; 2015.
217. Carpenter KJE. *Pellagra*. Vol. 2. London, England: Hutchinson Ross Publishing Company; 1981.
218. Etheridge EW. *The Butterfly Caste: A Social History of Pellagra in the South*. Westport, CT: Greenwood Publishing Company; 1972.
219. Glantz MH. *Drought and Hunger in Africa*. Cambridge, UK: Cambridge University Press; 1988.
220. Goldberger J. *Goldberger on Pellagra*. Baton Rouge, LA: Louisiana State University Press; 1964.
221. Harris S. *Clinical Pellagra*. Maryland Heights, MO: C. V. Mosby Company; 1941.
222. Iliffe J. *The African Poor: A History*. Cambridge, UK: Cambridge University Press; 1987.
223. Katz SH, Hediger ML, Valleroy LA. *Traditional Maize Processing Techniques in the New World*. Washington, DC: American Association for the Advancement of Science; 1974.
224. Kraut AM. *Goldberger's War: The Life and Work of a Public Health Crusader*. New York, NY: Farrar, Straus and Giroux; 2004.
225. Little PD. *The Elusive Granary: Herder, Farmer, and State in Northern Kenya*. Cambridge, UK: Cambridge University Press; 1992.
226. Lombroso C. *Trattato profilattico e clinico della pellagra*. Turin, Italy: Bocca; 1892.
227. Marie A. *Pellagra*. Sydney, NSW, Australia: Wentworth Press; 2016.
228. Niles GMC. *Pellagra: An American Problem*. Philadelphia, PA: W.B. Saunders Company; 1912.
229. Roberts SR. *Pellagra; History, Distribution, Diagnosis, Prognosis, Treatment, Etiology*. Sydney, NSW, Australia: Wentworth Press; 2016.
230. Roe DA. *A Plague of Corn: The Social History of Pellagra*. Ithaca, NY: Cornell University Press; 1973.
231. Salzman PC, Sadala E. *When Nomads Settle: Processes of Sedentarization as Adaptation and Response*. Westport, CT: Praeger; 1980.
232. Starling AP, Stock JT. Dental indicators of health and stress in early Egyptian and Nubian agriculturalists: a difficult transition and gradual recovery. *Am J Phys Anthropol*. 2007;134:520–528.
233. Watts MJ. *Silent Violence: Food, Famine, and Peasantry in Northern Nigeria*. Athens, GA: University of Georgia Press; 2013.
234. Hilliard SB. *Hog Meat and Hoeecake: A Geographical View of Food Supply in the Heart of the Old South, 1840–1860*. Madison, WI: University of Wisconsin–Madison; 1966.
235. Lucas WM. Perspectives in human malnutrition: a contribution to the biology of disease from a clinical and pathological study of chronic malnutrition and pellagra in the African. *J Natl Med Assoc*. 1952;44:241–242.
236. Pearce-Duvet JM. The origin of human pathogens: evaluating the role of agriculture and domestic animals in the evolution of human disease. *Biol Rev Camb Philos Soc*. 2006;81:369–382.
237. Doolittle WF, Booth A. It's the song, not the singer: an exploration of holobiosis and evolutionary theory. *Biol Philos*. 2017;32:5–24.
238. Warman A. *Corn & Capitalism: How a Botanical Bastard Grew to Global Dominance*. Chapel Hill, NC: University of North Carolina Press; 2003.
239. McCann J, McCann J. *Maize and Grace: Africa's Encounter with a New World Crop, 1500–2000*. Cambridge, MA: Harvard University Press; 2009.
240. White TCR. *The Inadequate Environment: Nitrogen and the Abundance of Animals*. Berlin, Germany: Springer; 2012.

241. Fogel RW. *The Escape from Hunger and Premature Death, 1700–2100: Europe, America, and the Third World*. Cambridge, UK: Cambridge University Press; 2004.
242. Brenton BP, Paine RR. Reevaluating the health and nutritional status of maize-dependent populations: evidence for the impact of pellagra on human skeletons from South Africa. *Ecol Food Nutr*. 2007;46:345–360.
243. Mann CC. *1491: New Revelations of the Americas before Columbus*. New York, NY: Vintage Books; 2006.
244. Fessler DM. Reproductive immunosuppression and diet. An evolutionary perspective on pregnancy sickness and meat consumption. *Curr Anthropol*. 2002;43:19–61.
245. Anderson M, Michael A. *British Population History: From the Black Death to the Present Day*. Cambridge, UK: Cambridge University Press; 1996.
246. Bashford A, Chaplin JE. *The New Worlds of Thomas Robert Malthus: Rereading the Principle of Population*. Princeton, NJ: Princeton University Press; 2016.
247. Camiscoli E. *Reproducing the French Race: Immigration, Intimacy, and Embodiment in the Early Twentieth Century*. Durham, NC: Duke University Press; 2009.
248. Coulmas F. *Population Decline and Ageing in Japan – The Social Consequences*. Abingdon, UK: Routledge; 2007.
249. Kaufmann EP. *Shall the Religious Inherit the Earth?: Demography and Politics in the Twenty-First Century*. London, England: Profile; 2010.
250. Kuznets S. Population and economic growth. *P Am Philos Soc*. 1967;111:170–193.
251. Poston DL, Yaukey D. *The Population of Modern China*. New York, NY: Springer; 2013.
252. Wilson C. Fertility below replacement level. *Science*. 2004;304:207–209.
253. Fuller DQ, Denham T, Arroyo-Kalin M, et al. Convergent evolution and parallelism in plant domestication revealed by an expanding archaeological record. *Proc Natl Acad Sci U S A*. 2014;111:6147–6152.
254. Edwards PC. Revising the Broad Spectrum Revolution: and its role in the origins of Southwest Asian food production. *Antiquity*. 1989;63:225–246.
255. Flannery KV. Origins and ecological effects of early domestication in Iran and the Near East. In: Ucko PJ, Dimbleby GW, eds. *The Domestication and Exploitation of Plants and Animals*. London, England: Gerald Duckworth & Co.; 1969:73–100.
256. Hublin JJ, Richards MP. *The Evolution of Hominin Diets: Integrating Approaches to the Study of Palaeolithic Subsistence*. Dordrecht, The Netherlands: Springer; 2009.
257. Jones EL. *In Search of the Broad Spectrum Revolution in Paleolithic Southwest Europe*. Cham, Switzerland: Springer International Publishing; 2015.
258. Weiss E, Wetterstrom W, Nadel D, Bar-Yosef O. The broad spectrum revisited: evidence from plant remains. *Proc Natl Acad Sci U S A*. 2004;101:9551–9555.
259. Pierre J, Appel B, Naji S. Testing the hypothesis of a worldwide neolithic demographic transition: corroboration from American cemeteries. *Curr Anthropol*. 2006;47:341–365.
260. Jacob HE, Winston C, Winston R. *Six Thousand Years of Bread: Its Holy and Unholy History*. New York, NY: Skyhorse Publishing Company, Incorporated; 2007.
261. Berbesque JC, Marlowe FW, Shaw P, Thompson P. Hunter–gatherers have less famine than agriculturalists. *Biol Lett*. 2014;10:20130853.
262. Mellars P. *Rethinking the Human Revolution: New Behavioural and Biological Perspectives on the Origin and Dispersal of Modern Humans*. Cambridge, UK: McDonald Institute for Archaeological Research; 2007.
263. Karkanas P, Koumouzelis M, Kozlowski JK, et al. The earliest evidence for clay hearths: Aurignacian features in Klisoura Cave 1, southern Greece. *Antiquity*. 2015;78:513–525.
264. Tilley CY. *A Phenomenology of Landscape: Places, Paths, and Monuments*. Oxford, UK: Berg; 1994.
265. Shennan S. *The First Farmers of Europe: An Evolutionary Perspective*. Cambridge, UK: Cambridge University Press; 2018.
266. Becker E. *The Denial of Death*. New York, NY: Free Press; 2007.
267. Nowak M, Highfield R. *SuperCooperators: Altruism, Evolution, and Why We Need Each Other to Succeed*. New York, NY: Free Press; 2011.
268. Braidwood RJ, Braidwood L. Jarmo: a village early farmers in Iraq. *Antiquity*. 1950;24:189–195.
269. Fort J. Synthesis between demic and cultural diffusion in the Neolithic transition in Europe. *Proc Natl Acad Sci U S A*. 2012;109:18669–18673.
270. Miles D. *The Tale of the Axe: How the Neolithic Revolution Transformed Britain*. London, England: Thames & Hudson; 2016.
271. Redman CL. *The Rise of Civilization: From Early Farmers to Urban Society in the Ancient Near East*. New York, NY: W. H. Freeman; 1978.
272. Whittle A, Cummings V, Academy B. *Going Over: The Mesolithic–Neolithic Transition in North West Europe*. New York, NY: Oxford University Press; 2007.
273. Henrich JP. *Foundations of Human Sociality: Economic Experiments and Ethnographic Evidence from Fifteen Small-Scale Societies*. Oxford, UK: Oxford University Press; 2004.
274. Kaplan HS, Hooper PL, Gurven M. The evolutionary and ecological roots of human social organization. *Philos Trans R Soc Lond B Biol Sci*. 2009;364:3289–3299.
275. Yudkin J. *Diet of Man, Needs and Wants*. London, England: Applied Science Publishers; 1978.
276. Powell A, Shennan S, Thomas MG. Late Pleistocene demography and the appearance of modern human behavior. *Science*. 2009;324:1298–1301.
277. Rutherford A. *The Book of Humans: The Story of How We Became Us*. London, England: Orion; 2018.
278. Mariotti Lippi M, Foggi B, Aranguren B, Ronchitelli A, Revedin A. Multistep food plant processing at Grotta Paglicci (Southern Italy) around 32,600 cal B.P. *Proc Natl Acad Sci U S A*. 2015;112:12075–12080.
279. Hodder I. *The Domestication of Europe*. London, England: Blackwell; 1990.
280. Wilson PJ. *The Domestication of the Human Species*. New Haven, CT: Yale University Press; 1991.
281. Ucko PJ, Tringham R, Dimbleby GW. *Man, Settlement and Urbanism*. London, England: Duckworth; 1972.
282. Notestein FW. Intrinsic factors in population growth. *P Am Philos Soc*. 1939;80:499–511.
283. Hagen EH, Barrett HC, Price ME. Do human parents face a quantity–quality tradeoff? evidence from a Shuar community. *Am J Phys Anthropol*. 2006;130:405–418.
284. Gaskins AJ, Chavarro JE. Diet and fertility: a review. *Am J Obstet Gynecol*. 2018;218:379–389.
285. Frisch RE. Population food intake and fertility. *Science*. 1978;199:22–30.
286. James Reynolds S, Schoech SJ, Bowman R. Diet quality during pre-laying and nestling periods influences growth and survival of Florida scrub-jay (*Aphelocoma coerulescens*) chicks. *J Zool*. 2003;261:217–226.
287. Pianka ER. *Evolutionary Ecology*. New York, NY: HarperCollins; 1994.
288. Vander Borgh M, Wyns C. Fertility and infertility: definition and epidemiology. *Clin Biochem*. 2018;62:2–10.
289. Promislow DE, Harvey PH. Living fast and dying young: a comparative analysis of life–history variation among mammals. *J Zool*. 1990;220:417–437.
290. McLaren IA. *Natural Regulation of Animal Populations*. Abingdon, UK: Routledge; 2017.
291. Cauvin J, Watkins T, Ashmore W, Gamble C, O'Shea J, Renfrew C. *The Birth of the Gods and the Origins of Agriculture*. Cambridge, UK: Cambridge University Press; 2000.
292. Atran S, Medin DL. *The Native Mind and the Cultural Construction of Nature*. Cambridge, MA: A Bradford Book; 2008.
293. Doubleday T. *The True Law of Population Shewn to be Connected with the Food of the People*. London, England: Simpkin, Marshall; 1842.
294. Aime C, Verdu P, Segurel L, et al. Microsatellite data show recent demographic expansions in sedentary but not in nomadic human populations in Africa and Eurasia. *Eur J Hum Genet*. 2014;22:1201–1207.
295. Suzman J. *Affluence without Abundance: The Disappearing World of the Bushmen*. London, England: Bloomsbury Publishing; 2017.
296. Hawks J, Hunley K, Lee S-H, Wolpoff M. Population bottlenecks and Pleistocene human evolution. *Mol Biol Evol*. 2000;17:2–22.
297. Klein RG. *The Human Career: Human Biological and Cultural Origins*. 3rd ed: Chicago, IL: University of Chicago Press; 2009.
298. Mithen S. *After the Ice: A Global Human History, 20,000–5000 BC*. Cambridge, MA: Harvard University Press; 2006.
299. Takahata N, Satta Y, Klein J. Divergence time and population size in the lineage leading to modern humans. *Theor Popul Biol*. 1995;48:198–221.
300. Silvertown J. *Dinner with Darwin: Food, Drink, and Evolution*. Chicago, IL: University of Chicago Press; 2017.
301. Marean CW. The transition to foraging for dense and predictable resources and its impact on the evolution of modern humans. *Philos Trans R Soc Lond B Biol Sci*. 2016;371.
302. Marean CW. Pinnacle Point Cave 13B (Western Cape Province, South Africa) in context: the Cape Floral kingdom, shellfish, and modern human origins. *J Hum Evol*. 2010;59:425–443.
303. Smith EI, Jacobs Z, Johnsen R, et al. Humans thrived in South Africa through the Toba eruption about 74,000 years ago. *Nature*. 2018;555:511–515.
304. Esteban I, Marean CW, Fisher EC, Karkanas P, Cabanes D, Albert RM. Phytoliths as an indicator of early modern humans plant gathering strategies, fire fuel and site occupation intensity during the Middle Stone Age at Pinnacle Point 5–6 (south coast, South Africa). *PLoS ONE*. 2018;13:e0198558.
305. Gibson MA, Mace R. Helpful grandmothers in rural Ethiopia: a study of the effect of kin on child survival and growth. *Evol Hum Behav*. 2005;26:469–482.
306. Balter M. *The Goddess and the Bull: Catalhöyük: An Archaeological Journey to the Dawn of Civilization*. Abingdon, UK: Routledge; 2016.
307. Eller C. *The Myth of Matriarchal Prehistory: Why an Invented Past Won't Give Women a Future*. Boston, MA: Beacon Press; 2000.
308. Fisher HE. *Anatomy of Love: A Natural History of Mating, Marriage, and Why We Stray*. New York, NY: Fawcett Columbine; 1994.
309. Goodison L, Morris C. *Ancient Goddesses: The Myths and the Evidence*. Madison, WI: University of Wisconsin Press; 1998.

310. Hodder I. *Archaeology beyond Dialogue*. Salt Lake City, UT: University of Utah Press; 2003.
311. Mellaart J. *The Archaeology of Ancient Turkey*. Lanham, MD: Rowman & Littlefield; 1978.
312. MacGregor N. *Living with the Gods: On Beliefs and Peoples*. London, England: Penguin Books; 2018.
313. Stearns SC. *The Evolution of Life Histories*. Oxford, UK: Oxford University Press; 1992.
314. Henshilwood CS, d'Errico F, Marean CW, Milo RG, Yates R. An early bone tool industry from the Middle Stone Age at Blombos Cave, South Africa: implications for the origins of modern human behaviour, symbolism and language. *J Hum Evol*. 2001;41:631–678.
315. Miller G. *The Mating Mind: How Sexual Choice Shaped the Evolution of Human Nature*. New York, NY: Vintage Books; 2001.
316. Bahn PG. *Images of the Ice Age*. Oxford, UK: Oxford University Press; 2016.
317. Gimbutas M. *The Goddesses and Gods of Old Europe, 6500–3500 BC, Myths and Cult Images*. Berkeley, CA: University of California Press; 1982.
318. Graziosi P. *Palaeolithic Art*. New York, NY: McGraw-Hill; 1960.
319. Laming A. *Lascaux: Paintings and Engravings*. London, England: Penguin Books; 1959.
320. Leroi-Gourhan A. *Gestures and Speech*. Cambridge, MA: MIT Press; 1993.
321. Buss DM. *The Evolution of Desire: Strategies of Human Mating*. New York, NY: Basic Books; 2016.
322. Cronin H, Smith JM. *The Ant and the Peacock: Altruism and Sexual Selection from Darwin to Today*. Cambridge, UK: Cambridge University Press; 1993.
323. De Block A, Dewitte S. Mating games: cultural evolution and sexual selection. *Biol Philos* 2007;22:475–491.
324. Gayon J. Sexual selection: another Darwinian process. *C R Biol*. 2010;333:134–144.
325. Prum RO. *The Evolution of Beauty: How Darwin's Forgotten Theory of Mate Choice Shapes the Animal World – and Us*. New York, NY: Knopf Doubleday Publishing Group; 2017.
326. Puts DA. Beauty and the beast: mechanisms of sexual selection in humans. *Evol Hum Behav*. 2010;31:157–175.
327. Richards E. *Darwin and the Making of Sexual Selection*. Chicago, IL: University of Chicago Press; 2017.
328. Shlain L. *Sex, Time, and Power: How Women's Sexuality Shaped Human Evolution*. London, England: Penguin Books; 2004.
329. Allport S. *The Primal Feast: Food, Sex, Foraging, and Love*. New York, NY: Open Road Integrated Media; 2016.
330. Symons D. *The Evolution of Human Sexuality*. Oxford, UK: Oxford University Press; 1979.
331. Thornhill R, Gangestad SW. *The Evolutionary Biology of Human Female Sexuality*. Oxford, UK: Oxford University Press; 2008.
332. Becker GS, Becker GS. *A Treatise on the Family*. Enlarged Edition. Cambridge, MA: Harvard University Press; 2009.
333. Blakemore SJ. The developing social brain: implications for education. *Neuron*. 2010;65:744–747.
334. Bowlby J. *Attachment and Loss*. New York, NY: Basic Books; 1980.
335. Carroll Mc CP. The Westermarck hypothesis and first cousin marriage: the cultural modification of negative sexual imprinting. *J Anthropol Res*. 1986;42:573–586.
336. Chagnon NA, Irons W, Association AA. *Evolutionary Biology and Human Social Behavior: An Anthropological Perspective*. Duxbury Press; 1979.
337. Dunbar RI. The social brain hypothesis and its implications for social evolution. *Ann Hum Biol*. 2009;36:562–572.
338. Hare B. Survival of the friendliest: *Homo sapiens* evolved via selection for prosociality. *Annu Rev Psychol*. 2017;68:155–186.
339. Kaplan H, Hill K, Lancaster J, Hurtado AM. A theory of human life history evolution: diet, intelligence, and longevity. *Evol Anthropol*. 2000;9:156–185.
340. Parker ST. A sexual selection model for hominid evolution. *Hum Evol*. 1987;2:235–253.
341. Pulliam HR, Dunford C. *Programmed to Learn: An Essay on the Evolution of Culture*. New York, NY: Columbia University Press; 1980.
342. Rosenthal GG. *Mate Choice: The Evolution of Sexual Decision Making from Microbes to Humans*. Princeton, NJ: Princeton University Press; 2017.
343. Dutton D. *The Art Instinct: Beauty, Pleasure, and Human Evolution*. London, England: Bloomsbury; 2010.
344. Collins D. *The Human Revolution: From Ape to Artist*. Oxford, UK: Phaidon; 1976.
345. Guthrie RD. *The Nature of Paleolithic Art*. Chicago, IL: University of Chicago Press; 2005.
346. Soffer O, Adovasio JM, Hyland DC, et al. The 'Venus' figurines: textiles, basketry, gender, and status in the Upper Paleolithic. *Curr Anthropol*. 2000;41:511–537.
347. Marshack A. *The Roots of Civilization: The Cognitive Beginnings of Man's First Art, Symbol and Notation*. New York, NY: Moyer Bell; 1991.
348. Sorokowski P, Sorokowska A, Butovskaya M, et al. Love influences reproductive success in humans. *Front Psychol*. 2017;8:1922.
349. Haselton MG, Mortezaie M, Pillsworth EG, Bleske-Rechek A, Frederick DA. Ovulatory shifts in human female ornamentation: near ovulation, women dress to impress. *Horm Behav*. 2007;51:40–45.
350. d'Errico F, Henshilwood C, Lawson G, et al. Archaeological evidence for the emergence of language, symbolism, and music – an alternative multidisciplinary perspective. *J World Prehist*. 2003;17:1–70.
351. Neal L. *The Earliest Instrument: Ritual Power and Fertility Magic of the Flute in Upper Paleolithic Culture*. Hillsdale, NY: Pendragon Press; 2015.
352. Geist V. *Life Strategies, Human Evolution, Environmental Design: Toward a Biological Theory of Health*. New York, NY: Springer; 2013.
353. Hrdy SB. *Mothers and Others*. Cambridge, MA: Harvard University Press; 2011.
354. Isler K, van Schaik CP. Allomaternal care, life history and brain size evolution in mammals. *J Hum Evol*. 2012;63:52–63.
355. Johnstone RA, Earle TK. *The Evolution of Human Societies: From Foraging Group to Agrarian State*. Stanford, CA: Stanford University Press; 2000.
356. El Zaatari S, Hublin JJ. Diet of upper paleolithic modern humans: evidence from microwear texture analysis. *Am J Phys Anthropol*. 2014;153:570–581.
357. Piperno DR, Weiss E, Holst I, Nadel D. Processing of wild cereal grains in the Upper Paleolithic revealed by starch grain analysis. *Nature*. 2004;430:670–673.
358. Revedin A, Aranguren B, Becattini R, et al. Thirty thousand-year-old evidence of plant food processing. *Proc Natl Acad Sci U S A*. 2010;107:18815–18819.
359. Ehlers J, Hughes P, Gibbard PL. *The Ice Age*. Hoboken, NJ: Wiley; 2016.
360. Dixson AF. *Sexual Selection and the Origins of Human Mating Systems*. Oxford, UK: Oxford University Press; 2009.
361. Soffer O, Gamble C. *The World at 18,000 BP: Low Latitudes*. London, England: Unwin Hyman; 1990.
362. Barber EW. *Women's Work: The First 20,000 Years Women, Cloth, and Society in Early Times*. New York, NY: W.W. Norton; 1995.
363. Hager L. *Women in Human Evolution*. London, England: Routledge; 2005.
364. Hoquet T. *Current Perspectives on Sexual Selection: What's left after Darwin?* Dordrecht, The Netherlands: Springer; 2015.
365. Kappeler PM, van Schaik CP. *Sexual Selection in Primates: New and Comparative Perspectives*. Cambridge, UK: Cambridge University Press; 2004.
366. Taylor T. *The Prehistory of Sex: Four Million Years of Human Sexual Culture*. London, England: Fourth Estate; 1997.
367. Renfrew C. *The Explanation of Culture Change. Models in Prehistory: Meeting, Sheffield, December 1971, Proceedings*. Pittsburgh, PA: University of Pittsburgh Press; 1973.
368. McBrearty S, Brooks AS. The revolution that wasn't: a new interpretation of the origin of modern human behavior. *J Hum Evol*. 2000;39:453–563.
369. Ward RH, Weiss KM. *The Demographic Evolution of Human Populations*. Cambridge, MA: Academic Press; 1976.
370. Roebroeks W. *Hunters of the Golden Age: The Mid Upper Palaeolithic of Eurasia, 30,000 – 20,000 BP*. Leiden, The Netherlands: University of Leiden; 1999.
371. Richards MP, Pettitt PB, Stiner MC, Trinkaus E. Stable isotope evidence for increasing dietary breadth in the European mid-Upper Paleolithic. *Proc Natl Acad Sci U S A*. 2001;98:6528–6532.
372. Starkovich BM. Paleolithic subsistence strategies and changes in site use at Klisoura Cave 1 (Peloponnese, Greece). *J Hum Evol*. 2017;111:63–84.
373. Puleston C, Tuljapurkar S, Winterhalder B. The invisible cliff: abrupt imposition of Malthusian Equilibrium in a natural-fertility, Agrarian Society. *PLoS ONE*. 2014;9:e87541.
374. Brody H. *Other Side of Eden: Hunters, Farmers and the Shaping of the World*. Madeira Park, BC, Canada: D & M Publishers; 2009.
375. Lev E, Kislev ME, Bar-Yosef O. Mousterian vegetal food in Kebara cave, Mt. Carmel. *J Archaeol Sci*. 2005;32:475–484.
376. Mithen S. *The Singing Neanderthals: The Origins of Music, Language, Mind and Body*. London, England: Orion; 2011.
377. Hardy BL, Moncel MH. Neanderthal use of fish, mammals, birds, starchy plants and wood 125–250,000 years ago. *PLoS ONE*. 2011;6:e23768.
378. Henry AG, Brooks AS, Piperno DR. Plant foods and the dietary ecology of Neanderthals and early modern humans. *J Hum Evol*. 2014;69:44–54.
379. Richards MP, Trinkaus E. Out of Africa: modern human origins special feature: isotopic evidence for the diets of European Neanderthals and early modern humans. *Proc Natl Acad Sci U S A*. 2009;106:16034–16039.
380. Marean CW, Assefa Z. Zooarchaeological evidence for the faunal exploitation behavior of Neanderthals and early modern humans. *Evol Anthropol*. 1999;8:22–37.
381. Finlayson C. *Neanderthals and Modern Humans: An Ecological and Evolutionary Perspective*. Cambridge, UK: Cambridge University Press; 2004.
382. Chikhi L, Destro-Bis G, Bertorelle G, Pascali V, Barbujani G. Clines of nuclear DNA markers suggest a largely Neolithic ancestry of the European gene pool. *Proc Natl Acad Sci U S A*. 1998;95:9053–9058.
383. Deevey ES Jr. The human population. *Sci Am*. 1960;203:195.

384. Berger TD, Trinkaus E. Patterns of trauma among the Neandertals. *J Archaeol Sci.* 1995;22:841–852.
385. Pettitt P, White M. *The British Palaeolithic: Hominin Societies at the Edge of the Pleistocene World*. New York, NY: Routledge; 2012.
386. Rogers AR, Bohlender RJ, Huff CD. Early history of Neanderthals and Denisovans. *Proc Natl Acad Sci U S A.* 2017;114:9859–9863.
387. Weyrich LS, Duchene S, Soubrier J, et al. Neanderthal behaviour, diet, and disease inferred from ancient DNA in dental calculus. *Nature.* 2017;544:357–361.
388. Lahr MM. *The Evolution of Modern Human Diversity: A Study of Cranial Variation*. Cambridge, UK: Cambridge University Press; 1996.
389. Otto G. Human evolution: archaic admixture with Denisovans. *Nat Rev Genet.* 2018;19:251.
390. Paabo S. The diverse origins of the human gene pool. *Nat Rev Genet.* 2015;16:313.
391. Sanchez-Quinto F, Lalueza-Fox C. Almost 20 years of Neanderthal palaeogenetics: adaptation, admixture, diversity, demography and extinction. *Philos Trans R Soc Lond B Biol Sci.* 2015;370:20130374.
392. Walker A, Zimmerman MR, Leakey RE. A possible case of hypervitaminosis A in *Homo erectus*. *Nature* 1982;296:248–250.
393. Wynn T, Coolidge FL. *How to Think Like a Neandertal*. New York, NY: Oxford University Press; 2011.
394. Barrett CB, Garg T, McBride L. *Well-Being Dynamics and Poverty Traps*. Leeds, UK: Centre for Climate Change Economics and Policy; 2016.
395. Gokhman D, Lavi E, Prufer K, et al. Reconstructing the DNA methylation maps of the Neanderthal and the Denisovan. *Science.* 2014;344:523–527.
396. Gokhman D, Malul A, Carmel L. Inferring past environments from ancient epigenomes. *Mol Biol Evol.* 2017;34:2429–2438.
397. Pennisi E. Epigenetics. Ancient DNA holds clues to gene activity in extinct humans. *Science.* 2014;344:245–246.
398. Bentley GR, Jasienska G, Goldberg T. Is the fertility of agriculturalists higher than that of nonagriculturalists? *Curr Anthropol.* 1993;34:778–785.
399. Mace R. Reproducing in cities. *Science.* 2008;319:764–766.
400. Senior AM, Lihoreau M, Buhl J, Raubenheimer D, Simpson SJ. Social network analysis and nutritional behavior: an integrated modeling approach. *Front Psychol.* 2016;7:18.
401. Kohler TA, Smith ME, Bogaard A, et al. Greater post-Neolithic wealth disparities in Eurasia than in North America and Mesoamerica. *Nature.* 2017;551:619–622.
402. Foley R, Gamble C. The ecology of social transitions in human evolution. *Philos Trans R Soc Lond B Biol Sci.* 2009;364:3267–3279.
403. Gamble C, Gowlett J, Dunbar R. The social brain and the shape of the Palaeolithic. *Camb Archaeol J.* 2011;21:115–136.
404. Wrangham RW. An ecological model of female-bonded primate groups. *Behaviour.* 1980;75:262–300.
405. Diamond J, Bellwood P. Farmers and their languages: the first expansions. *Science.* 2003;300:597–603.
406. Ehret C. Language family expansions: broadening our understandings of cause from an African perspective. In: Bellwood PS, Renfrew C, eds. *Examining the Farming/Language Dispersal Hypothesis*. Cambridge, UK: University of Cambridge; 2002:163–176.
407. Puchner M. *The Written World: How Literature Shaped History*. London, England: Granta Publications; 2017.
408. Renfrew C. *Archaeology and Language: The Puzzle of Indo-European Origins*. Cambridge, UK: Cambridge University Press; 1990.
409. Price TD, Feinman GM. *Foundations of Social Inequality*. New York, NY: Springer; 2013.
410. Henrich J. Demography and cultural evolution: how adaptive cultural processes can produce maladaptive losses – the Tasmanian case. *Am Antiquity.* 2004;69:197–214.
411. Cronon W. *Nature's Metropolis: Chicago and the Great West*. New York, NY: W.W. Norton; 2009.
412. Burger O, DeLong JP. What if fertility decline is not permanent? The need for an evolutionarily informed approach to understanding low fertility. *Philos Trans R Soc Lond B Biol Sci.* 2016;371:20150157.
413. Colleran H. The cultural evolution of fertility decline. *Philos Trans R Soc Lond B Biol Sci.* 2016;371:20150152.
414. Dribe M, Breschi M, Gagnon A, et al. Socio-economic status and fertility decline: insights from historical transitions in Europe and North America. *Popul Stud (Camb).* 2017;71:3–21.
415. Hruschka DJ, Burger O. How does variance in fertility change over the demographic transition? *Philos Trans R Soc Lond B Biol Sci.* 2016;371:20150155.
416. Page AE, Viguier S, Dyble M, et al. Reproductive trade-offs in extant hunter-gatherers suggest adaptive mechanism for the Neolithic expansion. *Proc Natl Acad Sci U S A.* 2016;113:4694–4699.
417. Wood JW. Fertility in anthropological populations. *Annu Rev Anthropol.* 1990;19:211–242.
418. Coleman D, Schofield R. *The State of Population Theory: Forward from Malthus*. Oxford, UK: Basil Blackwell; 1986.
419. Colleran H, Jasienska G, Nenko I, Galbarczyk A, Mace R. Fertility decline and the changing dynamics of wealth, status and inequality. *Proc Biol Sci.* 2015;282:20150287.
420. Lamba S, Mace R. Demography and ecology drive variation in cooperation across human populations. *Proc Natl Acad Sci U S A.* 2011;108:14426–14430.
421. Page AE, Chaudhary N, Viguier S, et al. Hunter-gatherer social networks and reproductive success. *Sci Rep.* 2017;7:1153.
422. Chang RQ, Li DJ, Li MQ. The role of indoleamine-2,3-dioxygenase in normal and pathological pregnancies. *Am J Reprod Immunol.* 2018;79:e12786.
423. Bach JF. The hygiene hypothesis in autoimmunity: the role of pathogens and commensals. *Nat Rev Immunol.* 2018;18:105–120.
424. de Laval B, Sieweke MH. Trained macrophages support hygiene hypothesis. *Nat Immunol.* 2017;18:1279.
425. De Rosa V, La Cava A, Matarese G. Metabolic pressure and the breach of immunological self-tolerance. *Nat Immunol.* 2017;18:1190–1196.
426. Ege MJ. The hygiene hypothesis in the age of the microbiome. *Ann Am Thorac Soc.* 2017;14:S348–S353.
427. Isolauri E, Huurre A, Salminen S, Impivaara O. The allergy epidemic extends beyond the past few decades. *Clin Exp Allergy.* 2004;34:1007–1010.
428. Khan TK, Palmer DJ, Prescott SL. In-utero exposures and the evolving epidemiology of paediatric allergy. *Curr Opin Allergy Clin Immunol.* 2015;15:402–408.
429. Lambrecht BN, Hammad H. The immunology of the allergy epidemic and the hygiene hypothesis. *Nat Immunol.* 2017;18:1076–1083.
430. Miftahussurur M, Nusi IA, Graham DY, Yamaoka Y. Helicobacter, hygiene, atopy, and asthma. *Front Microbiol.* 2017;8:1034.
431. Peters SE, Gaines RR. Formation of the 'Great Unconformity' as a trigger for the Cambrian explosion. *Nature.* 2012;484:363–366.
432. Santiago HC, Nutman TB. Human helminths and allergic disease: the hygiene hypothesis and beyond. *Am J Trop Med Hyg.* 2016;95:746–753.
433. Sokolowska M, Akdis CA. Highlights in immune response, microbiome and precision medicine in allergic disease and asthma. *Curr Opin Immunol.* 2017;48:iv–ix.
434. Ehlers S, Kaufmann SH. Infection, inflammation, and chronic diseases: consequences of a modern lifestyle. *Trends Immunol.* 2010;31:184–190.
435. Gerriets VA, Kishton RJ, Johnson MO, et al. Foxp3 and Toll-like receptor signaling balance Treg cell anabolic metabolism for suppression. *Nat Immunol.* 2016;17:1459–1466.
436. La Rocca C, Carbone F, De Rosa V, et al. Immunometabolic profiling of T cells from patients with relapsing-remitting multiple sclerosis reveals an impairment in glycolysis and mitochondrial respiration. *Metabolism.* 2017;77:39–46.
437. Ban Y, Chang Y, Dong B, Kong B, Qu X. Indoleamine 2, 3-dioxygenase levels at the normal and recurrent spontaneous abortion fetal-maternal interface. *J Int Med Res.* 2013;41:1135–1149.
438. McKenzie C, Tan J, Macia L, Mackay CR. The nutrition-gut microbiome-physiology axis and allergic diseases. *Immunol Rev.* 2017;278:277–295.
439. Mellor AL, Lemos H, Huang L. Indoleamine 2,3-dioxygenase and tolerance: where are we now? *Front Immunol.* 2017;8:1360.
440. Rook GA. Review series on helminths, immune modulation and the hygiene hypothesis: the broader implications of the hygiene hypothesis. *Immunology.* 2009;126:3–11.
441. Dieters R. *The Human Superorganism: How the Microbiome Is Revolutionizing the Pursuit of a Healthy Life*. London, England: Penguin Books; 2016.
442. Frodeman R, Klein JT, Pacheco RCDS. *The Oxford Handbook of Interdisciplinarity*. Oxford, UK: Oxford University Press; 2017.
443. Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature.* 2013;504:451.
444. Blaser M. *Missing Microbes*. London, England: Oneworld Publications; 2014.
445. Bollrath J, Powrie F. Feed your tregs more fiber. *Science.* 2013;341:463–464.
446. von Bubnoff D, Bieber T. The indoleamine 2, 3-dioxygenase (IDO) pathway controls allergy. *Allergy.* 2012;67:718–725.
447. Chang PV, Hao L, Offermanns S, Medzhitov R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. *Proc Natl Acad Sci U S A.* 2014;111:2247–2252.
448. Ciprandi G, Fuchs D. Tryptophan metabolic pathway, airway nitric oxide, and allergy. *Ann Allergy Asthma Immunol.* 2017;119:395–396.
449. Davis DM. *The Beautiful Cure: Harnessing Your Body's Natural Defences*. New York, NY: Random House; 2018.
450. Gostner JM, Becker K, Kofler H, Strasser B, Fuchs D. Tryptophan metabolism in allergic disorders. *Int Arch Allergy Immunol.* 2016;169:203–215.
451. Li Z, Li X, Lin S, et al. Nicotinic acid receptor GPR109A exerts anti-inflammatory effects through inhibiting the Akt/mTOR signaling pathway in MIN6 pancreatic beta cells. *Ann Clin Lab Sci.* 2017;47:729–737.
452. Matzinger P. Tolerance, danger, and the extended family. *Annu Rev Immunol.* 1994;12:991–1045.
453. Melnik BC. Milk – a nutrient system of mammalian evolution promoting mTORC1-dependent translation. *Int J Mol Sci.* 2015;16:17048–17087.

454. Sakaguchi S, Wing K, Miyara M. Regulatory T cells – a brief history and perspective. *Eur J Immunol*. 2007;37:S116–S123.
455. Shevach EM. The resurrection of T cell-mediated suppression. *J Immunol*. 2011;186:3805–3807.
456. Thornton AM, Shevach EM. CD4+ CD25+ immunoregulatory T cells suppress polyclonal T cell activation in vitro by inhibiting interleukin 2 production. *J Exp Med*. 1998;188:287–296.
457. Villeneuve C, Kou HH, Eckermann H, et al. Evolution of the hygiene hypothesis into biota alteration theory: what are the paradigms and where are the clinical applications? *Microbes Infect*. 2018;20:147–155.
458. Wu Z, Wang L, Tang Y, Sun X. Parasite-derived proteins for the treatment of allergies and autoimmune diseases. *Front Microbiol*. 2017;8:2164.
459. Carbone F, De Rosa V, Carrieri PB, et al. Regulatory T cell proliferative potential is impaired in human autoimmune disease. *Nat Med*. 2014;20:69–74.
460. Choi IY, Piccio L, Childress P, et al. A diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms. *Cell Rep*. 2016;15:2136–2146.
461. Manzel A, Muller DN, Hafler DA, Erdman SE, Linker RA, Kleinewietfeld M. Role of ‘Western diet’ in inflammatory autoimmune diseases. *Curr Allergy Asthma Rep*. 2014;14:404.
462. Xing X, Liao Z, Tan F, Zhu Z, Jiang Y, Cao Y. Effect of nicotinamide against *Candida albicans*. *Front Microbiol*. 2019;10:595.
463. Barkow JH, Burley N. Human fertility, evolutionary biology, and the demographic transition. *Ethol Sociobiol*. 1980;1:163–180.
464. Bookman MZ. *The Demographic Struggle for Power: The Political Economy of Demographic Engineering in the Modern World*. Abingdon, UK: Routledge; 2013.
465. Bremmer I. *The J Curve: A New Way to Understand Why Nations Rise and Fall*. New York, NY: Simon & Schuster; 2006.
466. Caldwell JC, Caldwell P. The cultural context of high fertility in sub-Saharan Africa. *Popul Dev Rev*. 1987;13:409–437.
467. Clark G. In defense of the Malthusian interpretation of history. *Eur Rev Econ Hist*. 2008;12:175–199.
468. Coole D. *Should We Control World Population?* Hoboken, NJ: Wiley; 2018.
469. Cullather N. *The Hungry World: America's Cold War Battle against Poverty in Asia*. Cambridge, MA: Harvard University Press; 2013.
470. Deaton A. *The Great Escape: Health, Wealth, and the Origins of Inequality*. Princeton, NJ: Princeton University Press; 2013.
471. Easterly W, Easterly WR. *The White Man's Burden: Why the West's Efforts to Aid the Rest Have Done So Much Ill and So Little Good*. London, England: Penguin Books; 2006.
472. Kenny C. *Getting Better: Why Global Development Is Succeeding – And How We Can Improve the World Even More*. New York, NY: Basic Books; 2012.
473. Lee R. The demographic transition: three centuries of fundamental change. *J Econ Perspect*. 2003;17:167–190.
474. Lesthaeghe R. The unfolding story of the second demographic transition. *Popul Dev Rev*. 2010;36:211–251.
475. Li H, Durbin R. Inference of human population history from individual whole-genome sequences. *Nature*. 2011;475:493.
476. Lutz W, Butz WP, Samir KC. *World Population and Human Capital in the Twenty-First Century: An Overview*. Oxford, UK: Oxford University Press; 2017.
477. Morland P. *The Human Tide: How Population Shaped the Modern World*. London, England: Hodder & Stoughton; 2019.
478. Pearson CS. *On the Cusp: From Population Boom to Bust*. Oxford, UK: Oxford University Press; 2015.
479. Sen A. *Development as Freedom*. Oxford, UK: Oxford University Press; 2001.
480. Van Den Bergh JCJM, Rietveld P. Reconsidering the limits to world population: meta-analysis and meta-prediction. *BioScience*. 2004;54:195–204.
481. Vitousek PM, Mooney HA, Lubchenco J, Melillo JM. Human domination of Earth's ecosystems. *Science*. 1997;277:494–499.
482. Katz SH. Food and biocultural evolution: a model for the investigation of modern nutritional problems. In: Johnston FE ed. *Nutritional Anthropology*. New York, NY: Alan R. Liss; 1987:41–63.
483. Cochran G, Harpending H. *The 10,000 Year Explosion: How Civilization Accelerated Human Evolution*. New York, NY: Basic Books; 2009.
484. Bauman Z. *Mortality, Immortality and Other Life Strategies*. Hoboken, NJ: Wiley; 2013.
485. Anthony DW. *The Horse, the Wheel, and Language: How Bronze-Age Riders from the Eurasian Steppes Shaped the Modern World*. Princeton, NJ: Princeton University Press; 2010.
486. Cunliffe B. *By Steppe, Desert, and Ocean: The Birth of Eurasia*. Oxford, UK: Oxford University Press; 2015.
487. Dunbar R. *The Human Story*. London, England: Faber & Faber; 2011.
488. Riley JC. *Rising Life Expectancy: A Global History*. Cambridge, UK: Cambridge University Press; 2001.
489. Shah NM, Herasimtschuk AA, Boasso A, et al. Changes in T cell and dendritic cell phenotype from mid to late pregnancy are indicative of a shift from immune tolerance to immune activation. *Front Immunol*. 2017;8:1138.
490. Everman ER, Morgan TJ. Antagonistic pleiotropy and mutation accumulation contribute to age-related decline in stress response. *Evolution*. 2018;72:303–317.
491. Patten MM. Selfish X chromosomes and speciation. *Mol Ecol*. 2018;27:3772–3782.
492. Presgraves DC. Evaluating genomic signatures of ‘the large X-effect’ during complex speciation. *Mol Ecol*. 2018;27:3822–3830.
493. Gibney MJ, Walsh MC. The future direction of personalised nutrition: my diet, my phenotype, my genes. *Proc Nutr Soc*. 2013;72:219–225.
494. Gorman U, Mathers JC, Grimaldi KA, Ahlgren J, Nordstrom K. Do we know enough? A scientific and ethical analysis of the basis for genetic-based personalized nutrition. *Genes Nutr*. 2013;8:373.
495. Stover PJ. Influence of human genetic variation on nutritional requirements. *Am J Clin Nutr*. 2006;83:436S–442S.
496. Stromland O, Niere M, Nikiforov AA, VanLinden MR, Heiland I, Ziegler M. Keeping the balance in NAD metabolism. *Biochem Soc Trans*. 2019;47:119–130.
497. Yaku K, Okabe K, Hikosaka K, Nakagawa T. NAD metabolism in cancer therapeutics. *Front Oncol*. 2018;8:622.
498. Neelakantan H, Brightwell CR, Graber TG, et al. Small molecule nicotinamide N-methyltransferase inhibitor activates senescent muscle stem cells and improves regenerative capacity of aged skeletal muscle. *Biochem Pharmacol*. 2019;163:481–492.
499. Poddar SK, Sifat AE, Haque S, Nahid NA, Chowdhury S, Mehedi I. Nicotinamide mononucleotide: exploration of diverse therapeutic applications of a potential molecule. *Biomolecules*. 2019;9:E34.
500. Rieff D. *The Reproach of Hunger: Food, Justice, and Money in the Twenty-First Century*. New York, NY: Simon & Schuster; 2016.
501. Zechner U, Wilda M, Kehrer-Sawatzki H, Vogel W, Fundele R, Hameister H. A high density of X-linked genes for general cognitive ability: a run-away process shaping human evolution? *Trends Genet*. 2001;17:697–701.